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Title:
Investigations Towards the Synthesis and Reactivity of 1,2-Bis(Boronic Esters) and its Application Towards the Total Synthesis of Bahamaolide A

Investigations Towards the Synthesis and Reactivity of 1,2-Bis(Boronic Esters) and its Application Towards the Total Synthesis of Bahamaolide A

University of BRISTOL

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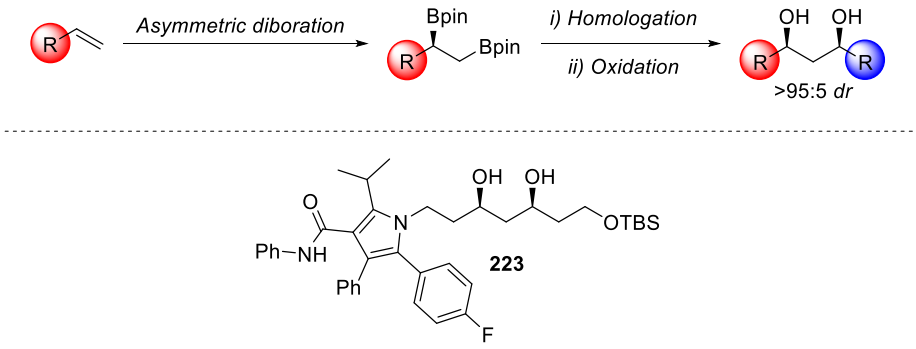
Abstract

This thesis documents the contributions made to four projects. Three of these projects explore the synthesis and reactivity of 1,2-bis(boronic esters), whereas the final project attempts to expand the scope of the Aggarwal group's lithiation–borylation methodology.

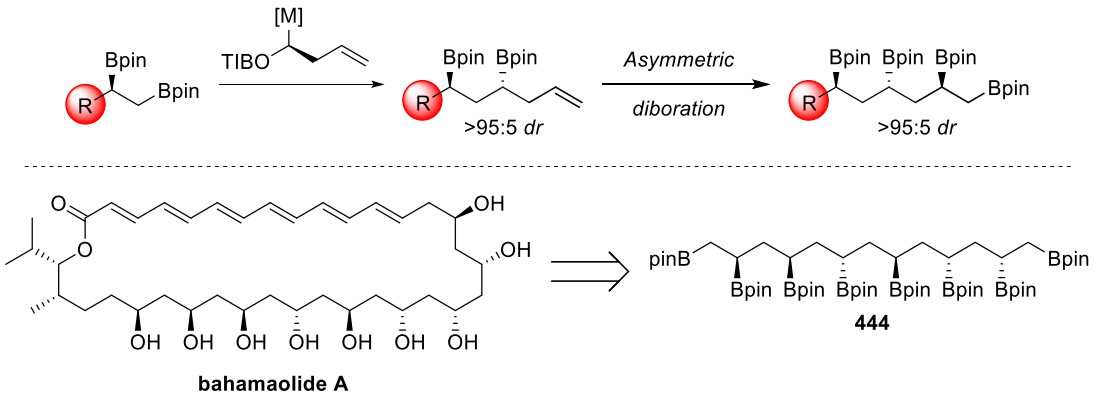
*Project 1: Synthesis of Atorvastatin derivative **223***

The Aggarwal group has shown that enantioenriched 1,2-bis(boronic esters) can be homologated selectively at the primary boronic ester with lithiated carbamates or benzoates to generate 1,3-bis(boronic esters), which can be oxidised to the corresponding 1,3-diols, in high diastereomeric excess.[1] This reagent-controlled process is able to access any stereochemical permutation of the 1,3-diol products without any matched or mismatched effects. The first project aimed to use this methodology to achieve a concise synthesis of compound **223**, which is a derivative of the blockbuster statin, atorvastatin.



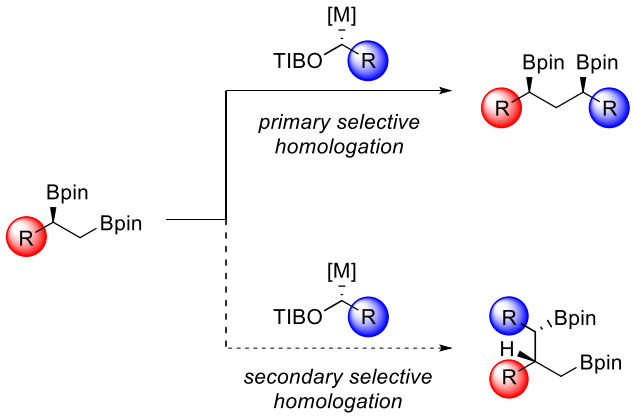
Project 2: Studies towards the total synthesis of bahamaolide A

1,3-Poly(boronic esters) can be obtained through an iterative diboration–homologation sequence when the homologation phase utilises a carbenoid with a pendent alkene. In the second project, we proposed to demonstrate the power of this methodology through the synthesis of the newly isolated oxopolyene macrolide, bahamaolide A.[2,3] The C_2 symmetric nature of the polyol portion of bahamaolide A led us to consider an iterative bi-directional strategy for its construction, where eight of the nine stereodefined hydroxyl groups would be revealed through the stereospecific oxidation of a carbon–boron bond. Our retrosynthetic analysis revealed C_2 symmetric octaboronic ester **444** as the key intermediate, which was made in only three steps from commercially available material.



Project 3: Studies towards a novel boronic ester protecting group

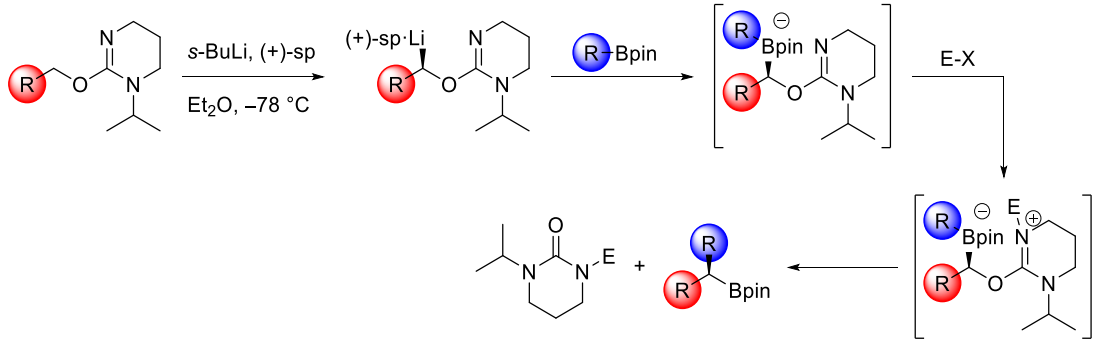
The third project was concerned with reversing the innate reactivity of a 1,2-bis(boronic ester) with a lithiated carbamate or benzoate by affording a regioselective homologation through the more hindered secondary boronic ester moiety. We rationalised that this could be achieved by lowering the Lewis acidity of the primary boronic ester relative to the secondary boronic ester by installing a suitable protecting group. Literature known protecting groups for boronic esters are incompatible with lithiation–borylation reactions and so a novel group was sought.



Project 4: Studies towards a new leaving group in lithiation–borylation reactions

The final project aimed to increase the scope of the lithiation–borylation reaction to include reaction partners that contain a strongly electronegative group, such as alkyl fluorides. Boronate complexes derived from a lithiated carbamate/benzoate with a boronic ester containing a strongly electron withdrawing substituent do not undergo the desired 1,2-metallate shift, but instead fragment to regenerate the boronic ester and lithiated species. We proposed that this limitation could be overcome by developing a

superior leaving group that would permit the 1,2-migration of a boronate complex before fragmentation.



Contents

Acknowledgements

First and foremost, I would like to thank Varinder for the incredible opportunity that he gave me. He has been an excellent role model and mentor, from whom I have learned so much. Varinder's enthusiasm and dedication to chemistry and his students both inspired and motivated and is a key ingredient of the success that our group enjoys. I am especially grateful for the level of responsibility that I was trusted with, which went far beyond what I felt I'd earned or deserved.

I would also like to thank Eddie Myers, who helped me immeasurably during the early phases of my PhD. Eddie had an exceptional level of empathy and knew exactly what each person needed to progress and be happy in the group. I am indebted to his commitment and support.

I have been fortunate to work with amazing people who made the lab such an enjoyable place to be. Some honourable mentions are, in no particular order, Fawcett, Stevie, Roy Mycucka, Felix and Sheenagh (collectively known as 'the boys'), Johan (my brother in chemistry), James, Siying, Dan, Lydia and Belen. At the end of my second year the group experienced a high turnover that saw most of the influential people from my first years leave. Again, in no particular order, I would like to mention Eddie, Cristina, Ana, Toby (Wurstesser), Alex Z, Olivier, Tong, Murat, DP, Hannah, Simon, Moritz, Damien, Alba, Paula, Giorgia and Rafael as the people who made the early years so fulfilling. I would also like to mention the group's 'super postdocs', Adam (now research officer), Alex Z, Beatrice and Roly who set the bar in group meetings and challenged us to rise to their level. I am indebted to those who proofread this thesis so diligently: Fawcett, Stevie, Rory, James, Sheenagh, Johan, Siying, Felix, Dan and Lydia.

In the twilight years of my PhD I was lucky enough to manage a small team working on poly(boronic ester) chemistry. I, of course, use the term 'manage' loosely as the other members, Sheenagh, Dabao and Selbi, are all exceptional chemists who taught me as much as I taught them. Thank you all for putting up with me.

My warmest thanks go to my family and friends who supported me throughout this journey. Marie, on a réussi. Je t'aime.

Finally, I would like to thank the ERC for funding.

Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirement of the University’s Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by a specific reference in the text, the work is the candidate’s own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE: .....

Abbreviations

acac	Acetylacetone
B	General base
Bus	*tert*-butylsulfonyl
cat	Catecholato
Cb	*N*,*N*-Diisopropylcarbamate
COD	1,5-Cyclooctadiene
CMBP	(Cyanomethyl)tributylphosphorane
CMMP	(Cyanomethyl)trimethylphosphorane
CPME	Cyclopentyl methyl ether
DABCO	1,4-diazabicyclo[2.2.2]octane
DAN	Diaminonaphthalene
dba	Dibenzylideneacetone
DCM	Dichloromethane
DIAD	Diisopropylazodicarboxylate
DICHED	Dicyclohexylethane-1,2-diol
DIPEA	*N*,*N*-Diisopropylethylamine
DIPED	Diisopropylethane-1,2-diol
DMP	Dess–Martin periodinane
DMAP	4-Dimethylaminopyridine
es	Enantiospecificity
E^+	General electrophile
EDG	Electron-donating group
EWG	Electron-withdrawing group
gly	Ethylene glycolato
Ipc	Isopinocampheol
LiDBB	Di-*tert*-butylbiphenylide
LTMP	Lithium tetramethylpiperidide
Me_4Phen	3,4,7,8-tetramethyl-1,10-phenanthroline
MIDA	*N*-methyliminodiacetic acid
NADPH	Nicotinamide adenine dinucleotide phosphate
neo	Neopentylglycolato

Nu	General nucleophile
pin	Pinacolato
PMDTA	Pentamethyldiethylenetriamine
PMP	*para*-Methoxyphenyl
PTSA	*para*-Toluenesulfonic acid
sp	Sparteine
sps	Sparteine surrogate
TBME	*tert*-Butyl methyl ether
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
TIB	2,4,6-Triisopropylbenzoate
TIBOH	2,4,6-Triisopropylbenzoic acid
TMEDA	*N,N,N',N*'-Tetramethlyethylenediamine
Tol	Tolyl

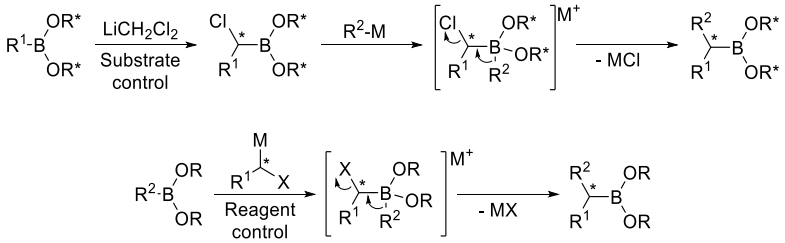
Introduction

This section has been adapted from a book chapter written by the author, which is to be published in an upcoming edition of PATAI'S Chemistry of Functional Groups.

The 1,2-metallate rearrangement of boronate complexes involves the migration of a boron bound R^1 group to an α-carbon atom with concomitant loss of an α-carbon bound nucleofuge, thus forming a new carbon–carbon or carbon–heteroatom bond (Scheme 1). This process requires anti-periplanar orientation of the migrating- and leaving groups, which renders the operation stereospecific, occurring with inversion of configuration at the α-carbon centre.[4] Of the metals and semimetals that can facilitate this transformation, boron is unique in its ability to execute this operation with exquisite levels of stereochemical fidelity.

Scheme 1 1,2-Metallate rearrangement of a boronate complex

The 1,2-metallate rearrangement is especially useful for making C─C bonds, which leads to a new boronic ester. Indeed, the new boronic ester can be homologated again and again, in an iterative manner, essentially growing the carbon chain one atom at a time. The homologation can be performed in an enantioselective fashion by incorporating a chiral ligand into the boronic ester component (substrate-control), or by utilizing an enantioenriched carbenoid species (reagent-control) (Scheme 2).



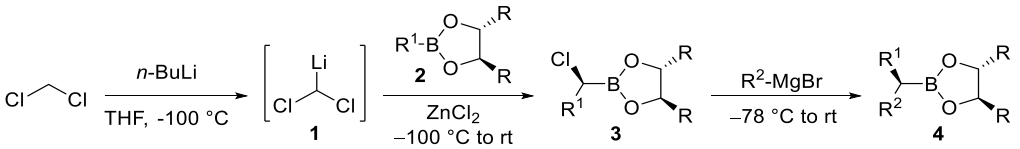
Scheme 2 Substrate- and reagent-controlled homologation of boronic esters

Substrate-controlled homologation of boronic esters

The Matteson Reaction

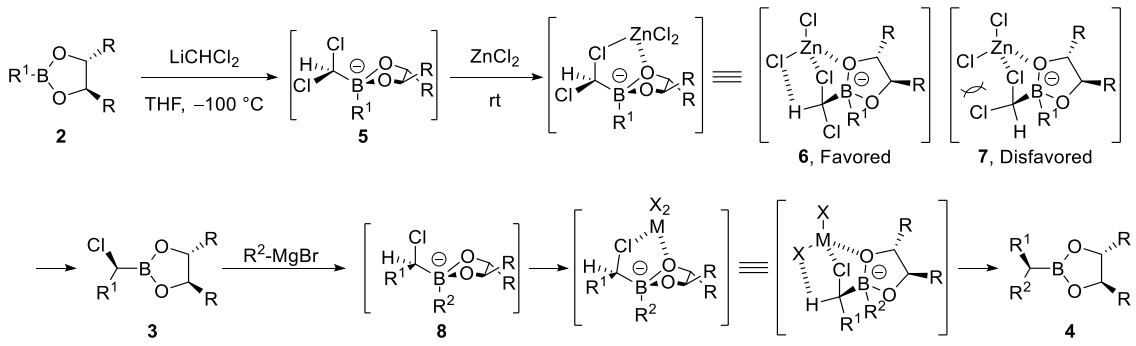
The Matteson reaction is the displacement of a leaving group from the α-carbon atom of an alkylboronic ester through addition of a nucleophile.[5] Typically, this reaction is

performed in an iterative two-step sequence, which begins with formation of α-chloro boronic ester **3** through homologation of alkylboronic ester **2** with (dichloromethyl)lithium (**1**), followed by invertive substitution of the α-halide through addition of a nucleophile to afford homologated boronic ester **4** (Scheme 3).[6] The product can be obtained with exquisite levels of diastereoselectivity (up to >99:1 *dr*) through the use of chiral diol ligands on boron and $ZnCl_2$ as an additive, where the diastereoselectivity is controlled by the stereochemical environment imparted by the chiral ligand.[7]



Scheme 3 The Matteson reaction

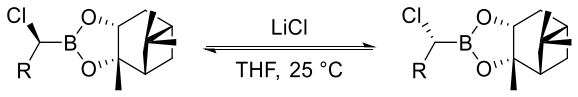
Corey proposed a model to account for the diastereoselectivity.[7] Addition of (dichloromethyl)lithium to alkylboronic ester **2** afforded boronate complex **5**. In the favoured case (transition state **6**), $ZnCl_2$ coordinated to the less hindered oxygen atom of the boronic ester moiety and to the pro-*R* chloride. There was also a further stabilising interaction between a chloride bound to $ZnCl_2$ and the proton at the α-boryl carbon centre. The coordination of $ZnCl_2$ placed the pro-*R* chloride anti-periplanar to the migrating R^1 group, thus facilitating migration. In the disfavoured case (transition state **7**), $ZnCl_2$ coordinated to the less hindered oxygen atom of the boronic ester and the pro-*S* chloride; however, the favourable chloride-proton interaction was replaced by an unfavourable steric interaction between two chlorides. Midland has shown through calculation that the difference in energy between transition states **6** and **7** is 12.6 kcal mol^{-1}.[8] Reaction of α-halo boronic ester **3** with a Grignard reagent gave boronate complex **8**, which underwent stereospecific 1,2-metallate rearrangement to afford secondary boronic ester **4** with inversion of stereochemistry at the α-carbon atom (Scheme 4).



Scheme 4 Origin of diastereoselectivity in the Matteson reaction

Several features of the reaction are worthy of note;

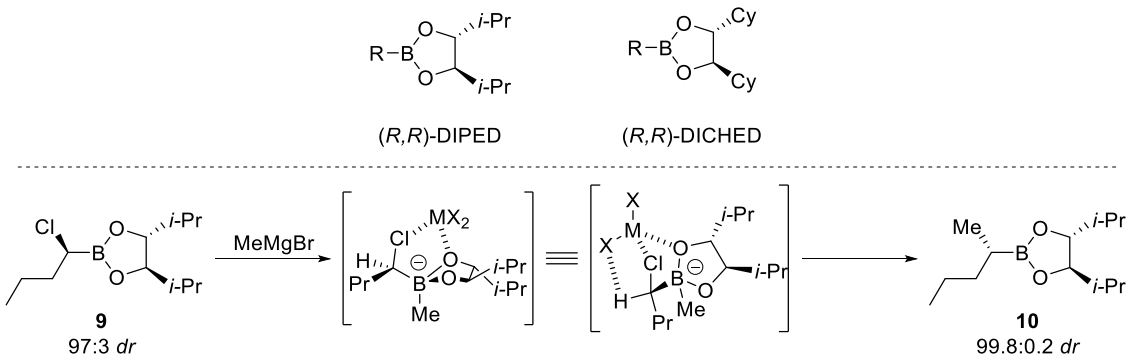
1) Boronate complex **5** was stable at –100 °C and did not undergo 1,2-metallate rearrangement until warmed to ambient temperature. (Dichloromethyl)lithium was unstable at temperatures above –100 °C and decomposed before 1,2-rearrangement occurred, thus preventing over homologation.
2) Upon addition of a Grignard reagent to α-chloroboronic ester **3**, boronate complex formation occurred exclusively. β-Elimination of the α-chloride was not observed.
3) α-Chloro boronic esters can undergo epimerization by chloride ions.[9] The epimerization event was found to have a 0.75-order dependence on lithium chloride, and was accelerated by water and DMSO. Therefore, quenching of the reaction with water prior to extraction led to a reduction in diastereoselectivity. Despite this, epimerization was avoided by quenching with a saturated solution of ammonium chloride, which was postulated to keep the boronic ester and LiCl in separate phases (Scheme 5).[10]



Scheme 5 Racemization of α-chloro boronic esters with LiCl

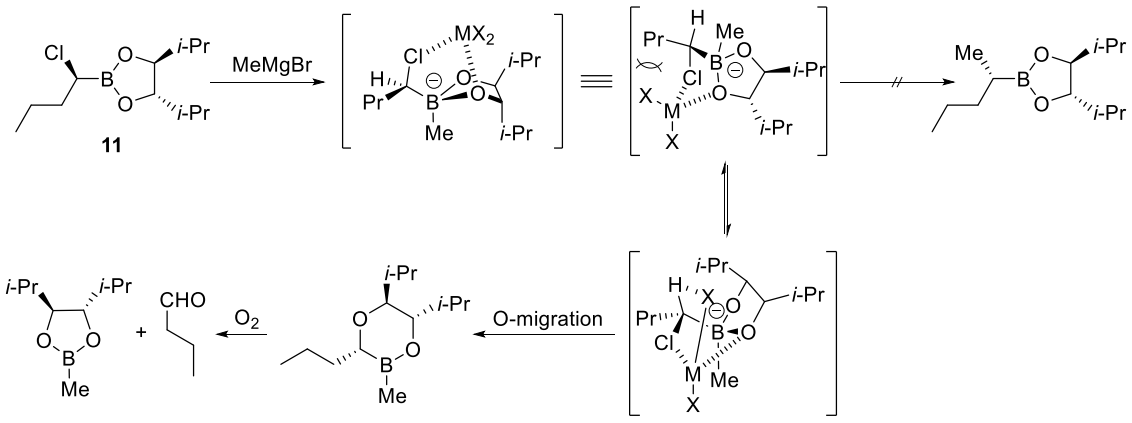
Sequential double stereodifferentiation with DIPED and DICHED

Matteson showed that diisopropylethanediol (DIPED)[11] and 1,2-dicyclohexylethane-1,2-diol (DICHED)[12] performed superbly in the asymmetric homologation of boronic esters, routinely giving superior diastereoselectivity to the corresponding pinanediol ligated boronic esters.[13] The reason for this enhanced stereoselectivity is that in certain cases C_2 symmetric boronic esters undergo sequential double stereodifferentiation, where the contra-kinetic diastereoisomer is discriminated against twice within the reaction sequence (Scheme 6).[14]



Scheme 6 Sequential double stereodifferentiation

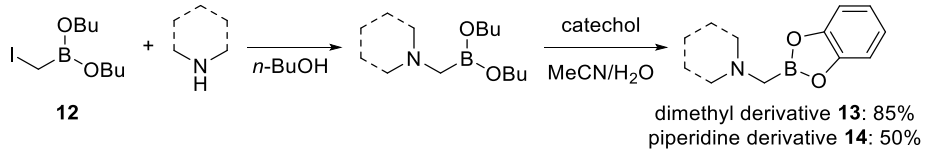
The conversion of α-chloroboronic ester **9** to boronic ester **10** was accompanied by an enrichment in diastereomeric ratio value (97:3 to 99.8:0.2 *dr*). In the case of the directed diastereoisomer, the 1,2-metallate rearrangement occurred efficiently through the expected transition state; however, the contra-kinetic diastereoisomer underwent contra-thermodynamic O-migration to afford a borinic ester, which decomposed upon isolation.[14] The contra-kinetic diastereoisomer was present in too small an amount to study so boronic ester **11** was synthesized through conversion of (*R*,*R*)-DIPED to (*S*,*S*)-DIPED. For this diastereoisomer, the interaction between the Lewis acid and the α-carbon bound proton is replaced with an unfavorable steric clash between the Lewis acid and the propyl group. Reorientation of the boronate complex to place one of the boronic ester oxygen atoms anti-periplanar to the departing chloride ion restored the stabilizing interaction between the Lewis acid and the α-carbon bound proton and alleviated the steric clash between the Lewis acid and propyl group, and resulted in O-migration (Scheme 7).[14] This phenomenon resulted in matched case homologations yielding products with very high diastereomeric ratio values.



Scheme 7 O-migration of contra-kinetic diastereoisomer

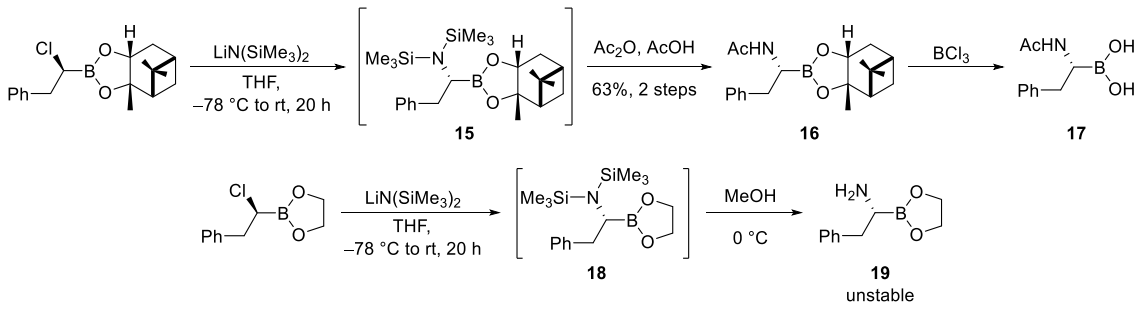
Migration of N-centred nucleophiles

The synthesis of tertiary α-amino boronic ester **13** from the reaction of dimethylamine with (iodomethyl)boronic ester **12** furnished **13** in 85% yield after transesterification with catechol.[15] Piperidine was also competent in this reaction, giving the corresponding tertiary α-amino boronic ester **14** in 50% yield. However, the reaction could not be expanded to the synthesis of primary or secondary α-amino boronic esters due to the instability of the products, which decomposed through a protodeboronation pathway (Scheme 8).



Scheme 8 Formation of α-amino boronic esters **13** and **14**

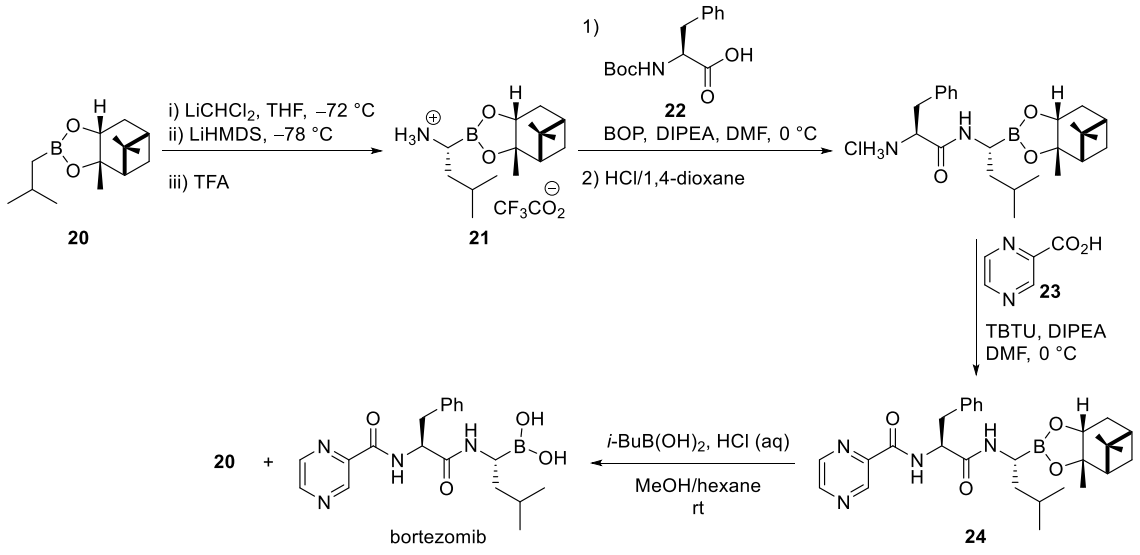
Synthesis of stable α-amino boronic ester derivatives was achieved by treatment of α-haloboronic esters with LiHMDS.[16,17,18] In this instance, 1,2-metallate rearrangement yielded silyl protected α-amino boronic ester **15**, which was isolated by distillation. Unprotected α-amino boronic ester **19** was accessed through silyl deprotection of **18** with methanol; however, **19** was unstable. Instead, the acetylated derivative **16** was targeted by treatment of **15** with acetic anhydride in acetic acid. Destructive removal of pinanediol with BCl_3 yielded optically pure (*R*)-α-amino boronic acid **17** (Scheme 9).[17] The (*S*)-enantiomer (**ent-17)** was prepared using the same sequence with (*R*)-pinanediol. Both (*R*)- and (*S*)-enantiomers were potent inhibitors of the serine protease chymotrypsin, with the (*R*)-enantiomer being more active than the (*S*)-enantiomer.[17]



Scheme 9 Synthesis of stable α-amino boronic ester derivatives

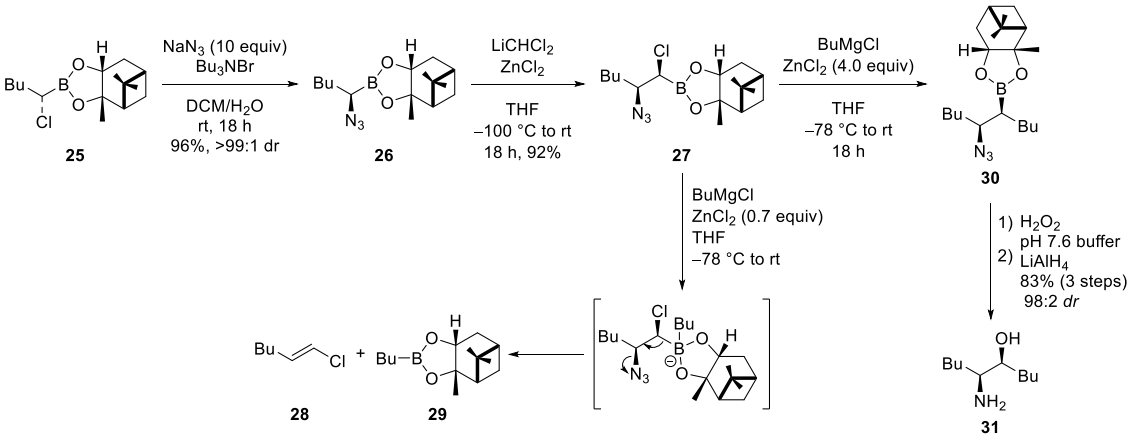
This methodology was used by Adams in the first synthesis of the serine protease inhibitor bortezomib,[19] which is marketed as Valcade® by Takeda Oncology for the treatment of multiple myeloma.[20–22] Disconnection of the amide bonds revealed pyrazinoyl moiety **23**,

L-phenylalanine (**22**) and L-boronoleucine (**21**), which was assembled from isobutyl boronic ester **20** using Mattson's homologation methodology.[23] An efficient deprotection of pinanediol boronic ester **24** by transesterification with isobutyl boronic acid gave bortezomib and regenerated boronic ester **20** (Scheme 10).



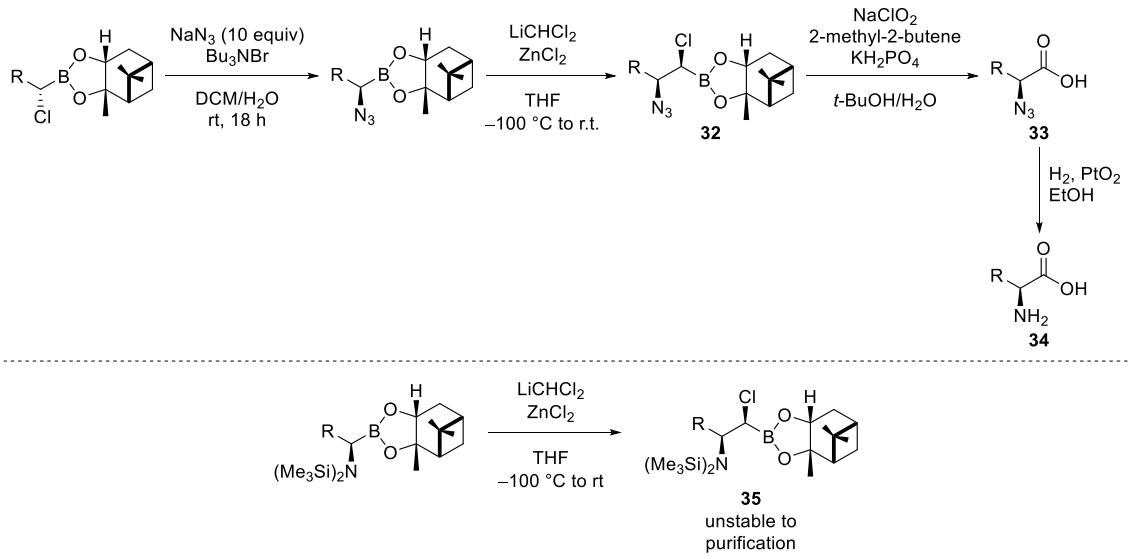
Scheme 10 Synthesis of bortezomib

Azides are also competent nucleophiles in the displacement of α-boryl chloride ions. Treatment of α-chloroboronic ester **25** with sodium azide generated the stable α-azoboronic ester **26**.[10] Despite its stability, **26** was especially susceptible to LiCl mediated epimerization. To prevent unwanted epimerization, boronic ester **25** was added to a ten-equivalent excess of sodium azide in dichloromethane/water with a tetrabutylammonium phase transfer catalyst, which permitted the isolation of α-azoboronic ester **26** with >99:1 *dr*. Homologation of **26** with (dichloromethyl)lithium proceeded smoothly to yield α-chloroboronic ester **27**; however, subsequent addition of butyl magnesium chloride resulted in β-elimination leading to butyl boronic ester **29** and material characterized as having an alkene, which would presumably have the structure of **28**. The desired product was obtained through the addition of excess $ZnCl_2$, which promoted 1,2-migration over elimination. Oxidation of boronic ester **30** at pH 7.6 and subsequent reduction of the diazo moiety with LiAlH yielded vicinal amino alcohol **31** (Scheme 11).[10]



Scheme 11 Azides as nucleophiles in the Matteson reaction

The displacement reaction of α-chloroboronic esters has also been applied to the synthesis of amino acids.[24] A facile 1 step oxidation of α-chloroboronic ester **32** to carboxylic acid **33** was achieved by treatment with $NaClO_2$. Subsequent reduction of **33** by hydrogenation over a Pt catalyst yielded enantiopure (*S*)-amino acid **34** (Scheme 12).[24] Using this methodology, Matteson was able to synthesise phenylalanine, valine, serine and glutamic acid. The synthesis of α-amino derivates with sodium azide proved to be superior than when using LiHMDS, due to the instability of the β-silylamino α-chloro boronic ester **35**, which was formed after a further homologation with (dichloromethyl)lithium.[24]

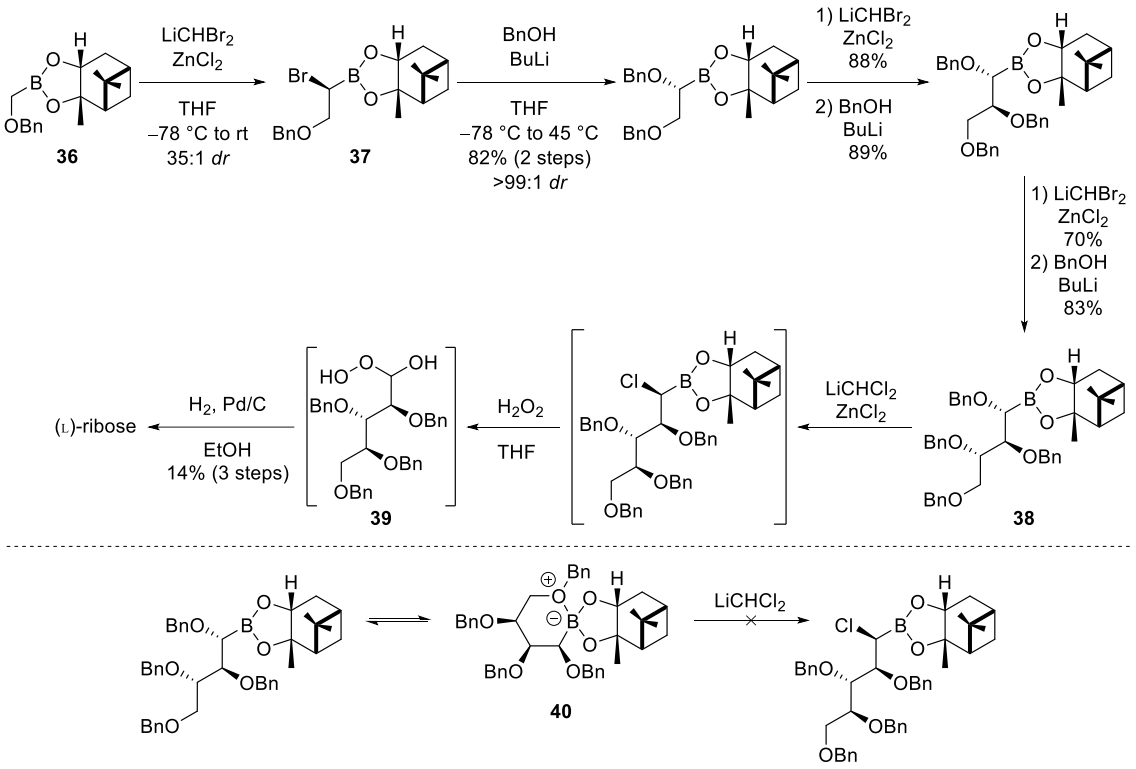


Scheme 12 Synthesis of amino acids using the Matteson reaction

Migration of O-centred nucleophiles

Matteson has shown that *O*-centred nucleophiles participate in 1,2-metallate rearrangement reactions to yield protected α-hydroxy boronic esters.[10] The rate and diastereoselectivity of alkoxy group migration is reduced by preferential coordination of

$ZnCl_2$ to the oxygen atom of the migrating group.[25] To overcome this limitation a slight excess of $ZnCl_2$ is required,[10] although addition of superfluous amounts of $ZnCl_2$ resulted in enhanced epimerization of the products by $ZnCl_2$ and $LiZnCl_3$.[9] The optimum loading of $ZnCl_2$ was found to be 1.0 equiv for each alkoxy substituent and an additional 0.7 equiv for catalysis. The limit of iterative installation of contiguous benzyloxy substituents was realized during the synthesis of (L)-ribose (Scheme 13).[25]

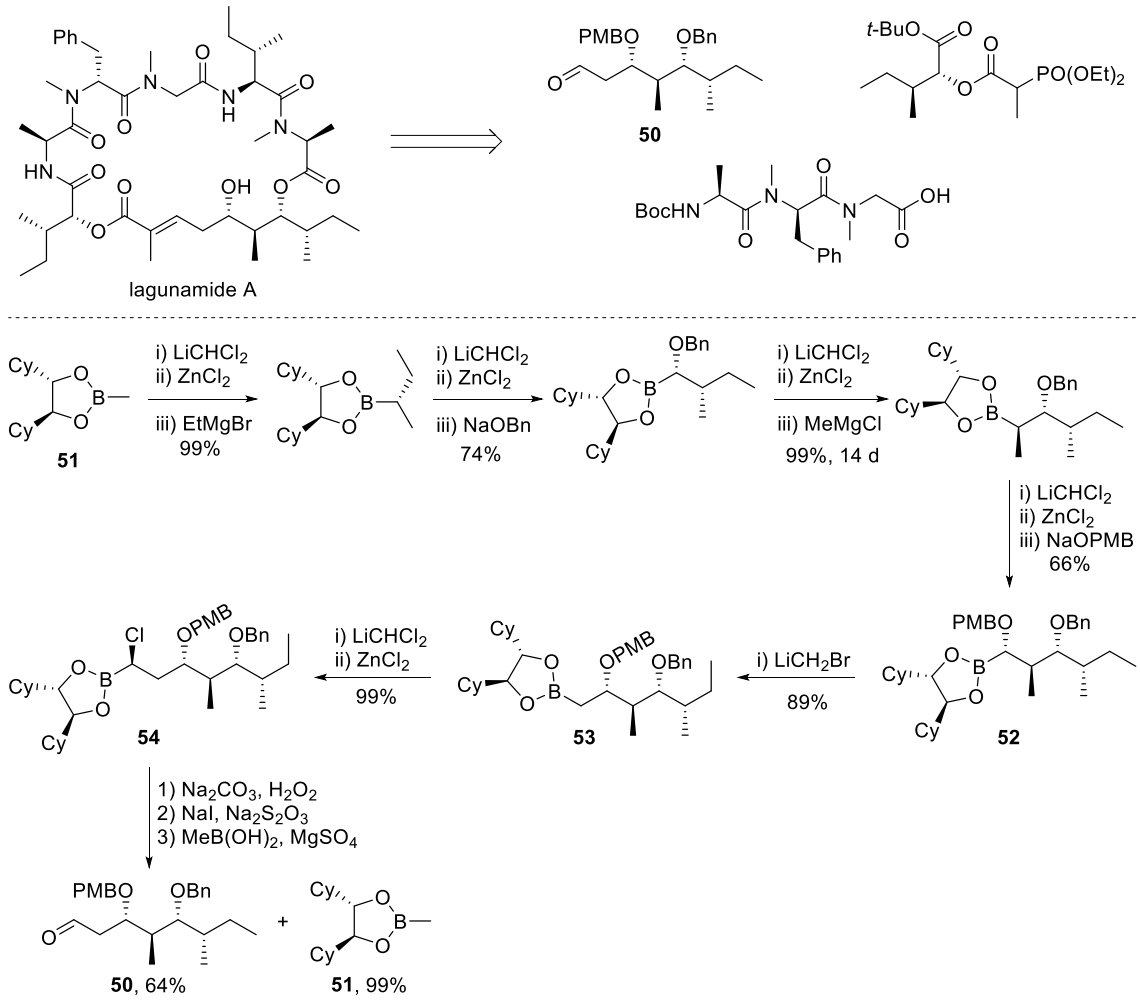


Scheme 13 Synthesis of (L)-ribose

In this case, the use of α-bromoboronic esters, such as **37**, resulted in superior yields and diastereomeric ratios than the corresponding α-chloroboronic esters. Advanced intermediate **38** was obtained in six iterative steps from benzyloxy boronic ester **36**. Homologation of boronic ester **38** with both (dibromomethyl)lithium and (dichloromethyl)lithium gave an intractable mixture; however, peroxide–aldehyde adduct **39** was observed in poor yield after oxidation with hydrogen peroxide following homologation with (dichloromethyl)lithium. Hydrogenation with palladium over carbon yielded (L)-ribose. The difficulties in installing the final carbon atom were attributed to the steric bulk of the system; however, more recently Hirschhäuser and coworkers have suggested that formation of six-membered intramolecular boronate complex **40** impedes further homologation by preventing formation of a further boronate complex (Scheme 13).[26,27]

Recent applications of the Matteson reaction in total synthesis

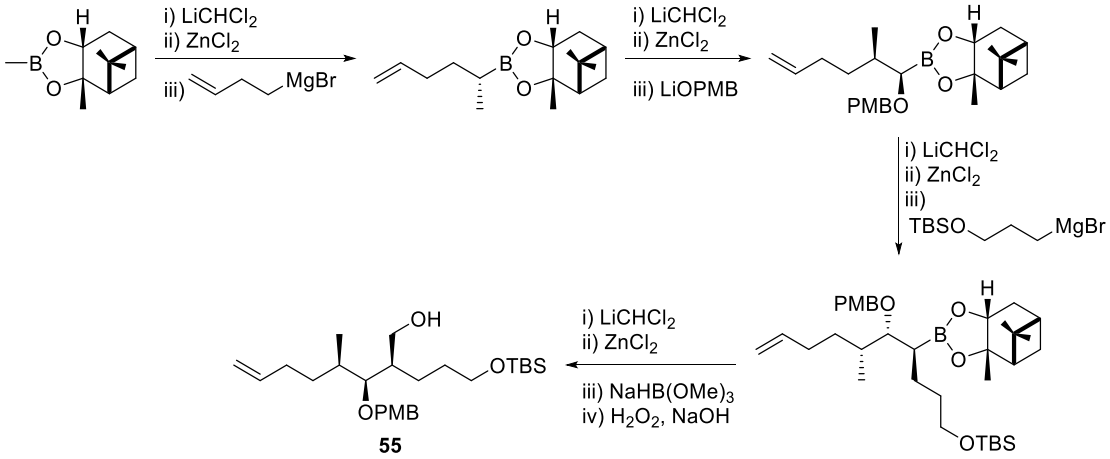
Kazmeier reported the synthesis of polyketide fragment **50** as an advanced intermediate in the synthesis of lagunamide A using six sequential Matteson homologation steps followed by oxidation (Scheme 14).[28] Synthesis of intermediate **52** from methyl boronic ester **51** proceeded smoothly; however, homologation of **52** with $LiCH_2Cl$ failed to generate boronic ester **53**. The solution to this problem was to employ $LiCH_2Br$ as the homologating agent and to ensure that the reaction temperature was strictly maintained at –60 °C, which permitted the formation of **53** in 89% yield. A further homologation gave α-chloro boronic ester **54**, which was transformed to aldehyde **50** in high yield. The chiral ligand was recovered in quantitative yield through addition of methyl boronic acid to regenerate methyl boronic ester **51**.



Scheme 14 Synthesis of aldehyde **50** as an intermediate in the synthesis of lagunamide A

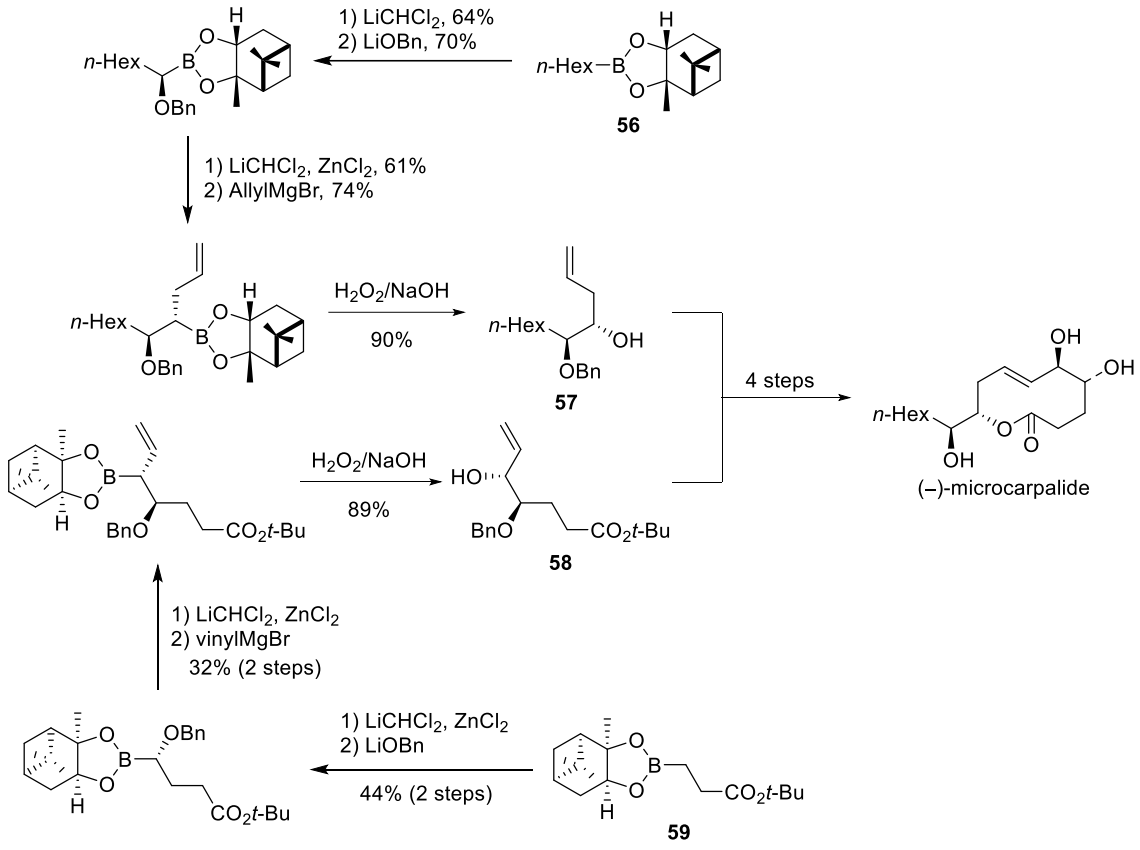
Armstrong applied the Matteson homologation reaction to the synthesis of intermediate **55** in his synthesis of the C1–C21 fragment of the serine/threonine phosphatase inhibitor

tautomycin (Scheme 15).[29,30] Compound **55** was obtained after three iterative Matteson homologation steps, a further homologation with (dichloromethyl)lithium, de-chlorination of the resulting α-chloro boronic ester with sodium trimethoxyborohydride and oxidation.



Scheme 15 Synthesis of alkene 55 as an intermediate in the synthesis of the C1–C21 fragment of tautomycin

Davoli showed the convergent synthesis of (–)-microcarpalide in which fragments **57** and **58** were both prepared using substrate-controlled homologations of boronic esters (Scheme 16).[33,34] Homoallylic alcohol **57** was obtained from boronic ester **56** following two homologation steps and oxidation. Allylic alcohol **58** was obtained through a similar sequence from boronic ester **59**. The synthesis of (–)-microcarpalide was completed in a further four steps.



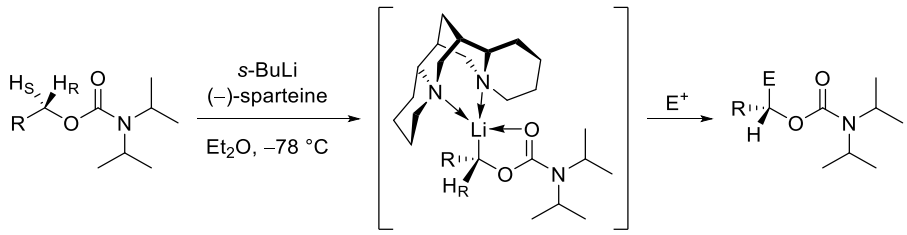
Scheme 16 Synthesis of (–)-microcarpalide

Reagent-controlled homologation of boronic esters

Reagent-controlled homologation has the advantage over substrate-controlled homologation in that either enantiomer/diastereoisomer of the product can be obtained by selecting the appropriate enantiomorph of the chiral reagent, whereas in a substrate-controlled process a two-step sequence to exchange the enantiomer of chiral ligand must be performed prior to homologation. For a reagent-controlled homologation of boronic esters to be successful a number of criteria must be fulfilled: (i) the chiral reagent must be chemically and configurationally stable under the reaction conditions (ii) the formation of the boronate complex and the subsequent 1,2-metallate rearrangement must be stereospecific (iii) any excess carbenoid must decompose prior to 1,2-metallate rearrangement to prevent over-homologation (iv) the stereoselectivity of the reaction should not be influenced by stereogenic centres already present in either the carbenoid or the boronic ester.

Homologation of Boronic Esters with Lithiated Carbamates and Benzoates

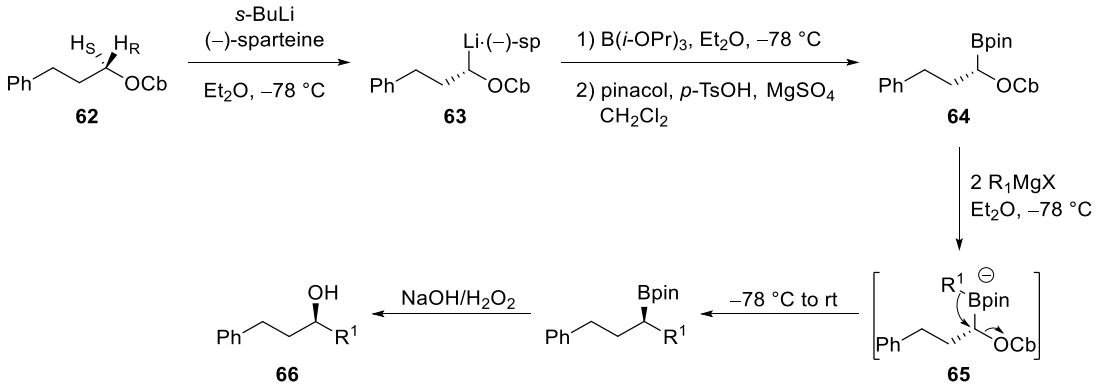
Enantioselective deprotonation of Hoppe-type carbamates[33] and Beak-type triisopropylbenzoates[34] gives dipole stabilized carbanions. These intermediates fulfil the criteria required for reagent-controlled homologation. Specifically, when treated with *s*-BuLi and (–)-sparteine, *O*-alkylcarbamates and triisopropylbenzoates undergo reagent-controlled deprotonation of the pro-*S*-proton. The resulting lithium carbenoid is chemically and configurationally stable at –78 ˚C and can be trapped with electrophiles with retention of stereochemistry (Scheme 17).



Scheme 17 Asymmetric deprotonation of an O-alkyl carbamate with *s*-BuLi and (+)-sparteine.

Hoppe showed the first example of a reagent-controlled homologation of boronic esters with the conversion of primary *O*-alkylcarbamates to enantioenriched secondary alcohols in a two-step process. Specifically, deprotonation of carbamate **62** with *s*-BuLi/(–)-sparteine generated lithiated carbamate **63**. Treatment of **63** with triisopropyl borate resulted in electrophilic trapping with retention of configuration to yield boronic ester **64** in 95% *ee* after transesterification with pinacol.[35] Addition of a Grignard reagent

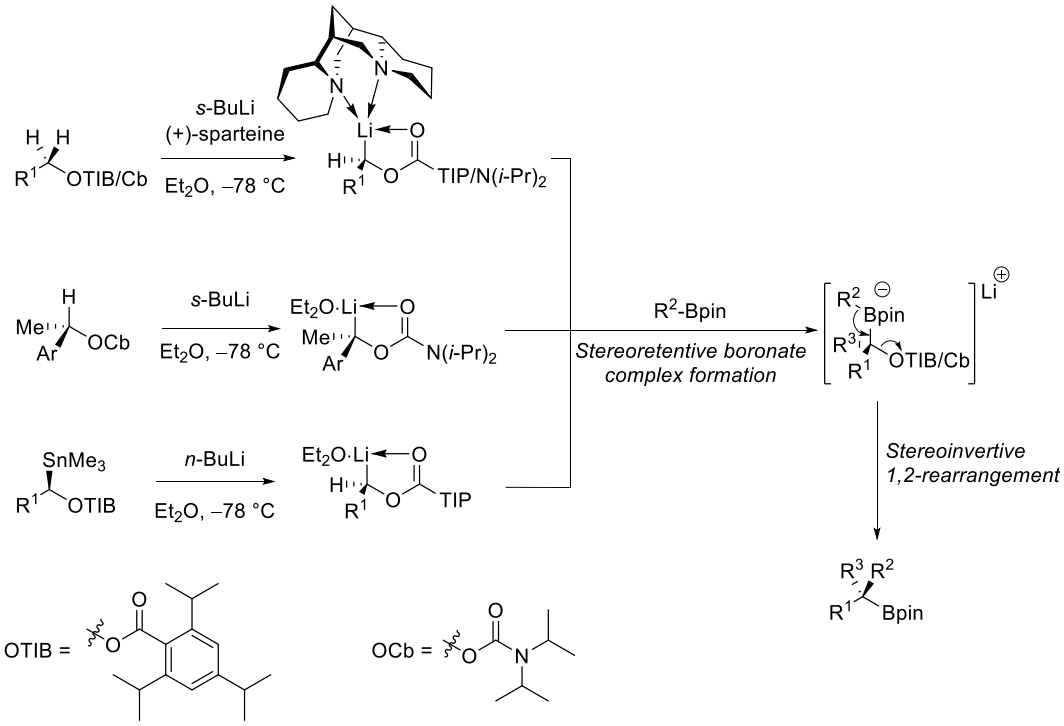
to **64** at –78 ˚C formed boronate complex **65**, which underwent stereospecific 1,2-metallate rearrangement with inversion of configuration upon warming the reaction mixture to room temperature, yielding secondary alcohol **66** after oxidation (Scheme 18).



Scheme 18 Hoppe's reagent-controlled homologation of boronic esters

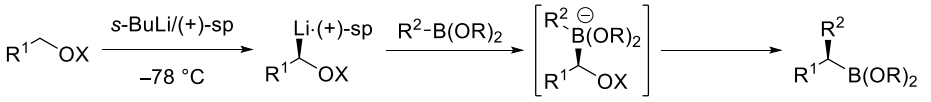
The Lithiation–Borylation Reaction

Lithiation–borylation is the colloquial description of the homologation of boronic esters with lithiated carbamates and benzoates, which has been extensively developed by the Aggarwal group.[36] The reaction consists of three phases; (i) the generation of a lithiated carbenoid through the enantioselective or enantiospecific deprotonation of a suitable carbamate or benzoate, or through the stereospecific tin–lithium exchange of an enantioenriched α-stannyl benzoate, (ii) the stereoretentive formation of a boronate complex, (iii) the stereoinvertive 1,2-metallate rearrangement of the boronate complex to yield a homologated boronic ester with concomitant expulsion of the carbamate or benzoate nucleofuge (Scheme 19).

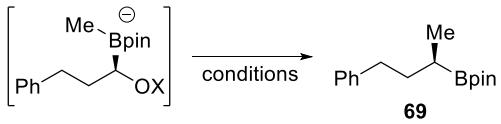


Scheme 19 The lithiation–borylation reaction

The rates of lithiation, borylation and migration are impacted by the identity of the directing group, the solvent, the diamine and steric hinderance at the β-position of the carbamate/benzoate.[37] Lithiation of benzoates with *s*-BuLi and (+)-sparteine occurred two to three times faster than the corresponding carbamates due to a parasitic interaction between the carbamate, *s*-BuLi and (+)-sparteine, which was observable through *in situ* IR spectroscopy.[37] No such interaction was detected upon lithiation of a benzoate; however, borylation of a lithiated carbamate occurred more rapidly than the corresponding lithiated benzoate, which was attributed to a steric effect.[37] The rate of 1,2-migration was faster in the case of benzoates than carbamates, which permitted challenging migrating groups, such as methyl, to be tolerated in lithiation–borylation reactions.[38] Specifically, when carbamate derived boronate complex **67** was reacted at 35 °C for 16 h the expected boronic ester was obtained in less than 10% yield. The addition of $MgBr_2{\cdot}Et_2O$ improved the yield to 50%; however, employing benzoate derived boronate complex **68** furnished boronic ester **69** in 76% yield after 2 h at 35 °C without the addition of an additive (Scheme 20).[38]



X	Solvent	Lithiation	Borylation	Migration
Cb	Et_2O	Slow	Fast	Slow
TIB	Et_2O	Fast	Slow	Fast
Cb	PhMe	Very slow	Very slow	Slow
TIB	PhMe	Very fast	Very slow	Fast



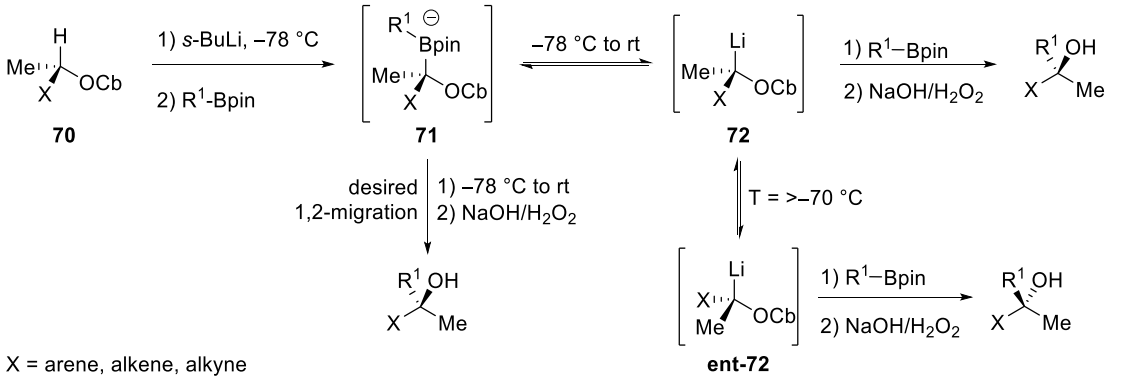
69

X	Conditions	yield (%)	*er*
Cb	35 °C, 16 h	< 10	n.d.
	$MgBr_2·Et_2O$, 35 °C, 16 h	50	95:5
TIB	35 °C, 2 h	76	96:4

Scheme 20 Differences between carbamates and benzoates in the lithiation–borylation reaction

Synthesis of tertiary boronic esters

Aggarwal has shown the synthesis of tertiary benzylic,[47,48] allylic,[41] propargylic,[42] and dialkyl[43] boronic esters through lithiation–borylation reactions with suitable enantioenriched secondary carbamates or benzoates. The reaction proceeded by initial deprotonation of the enantioenriched carbenoid precursor **70** and subsequent addition of a boronic ester, which generated boronate complex **71**. The reaction was then warmed to ambient temperature to permit 1,2-metallate rearrangement; however, due to the hindered nature of the boronate complex and the relatively low nucleofugality of carbamates, the 1,2-migration was slow.[40] As a result, when the carbamate contained an arene, alkene or alkyne in the α-position, a competing process occurred where boronate complex **71** reversibly fragmented at elevated temperature and regenerated stabilized organolithium species **72**, which was not configurationally stable above –70 °C.[40] Partial racemization of **72** occurred before recombination with the boronic ester, which afforded a boronate complex of undesired configuration, which subsequently migrated to yield the enantiomeric boronic ester (Scheme 21).[40]

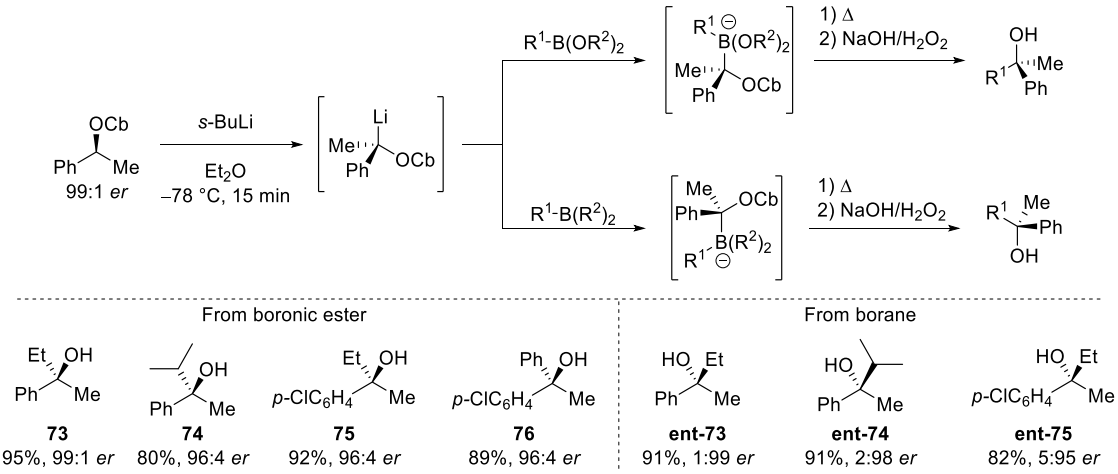


Scheme 21 Reversible fragmentation of boronate complexes leads to products with diminished *ee* values

This issue was resolved through the addition of a second electrophile—which reacts with the carbenoid irreversibly—before warming to ambient temperature. The optimal electrophile was $MgBr_2$·MeOH,[40] which permitted the formation of tertiary alcohols in high yield and enantiomeric excess, even when using sterically hindered or electron withdrawing reaction partners. The role of $MgBr_2$·MeOH is two-fold; firstly, coordination of $MgBr_2$ to the carbamate makes it a better leaving group, which promotes the desired 1,2-migration over fragmentation. Additionally, any lithiated species generated by the reversible fragmentation of the boronate complex is immediately quenched by MeOH, thus preventing recombination with the boronic ester.[40]

1,2-Rearrangement of boronate complexes can be applied to the enantiodivergent synthesis of tertiary alcohols from enantioenriched secondary alcohols.[39] Secondary benzylic carbamates—derived from the corresponding enantiopure secondary benzylic alcohol—can be lithiated with *s*-BuLi to generate a benzylic carbenoid that is configurationally stable at –78 ˚C. Retentive trapping of a boronic ester, 1,2-rearrangement and subsequent oxidation yields an enantioenriched tertiary alcohol. Interestingly, if the same benzylic carbenoid is treated with a trialkyl borane, electrophilic trapping occurs with inversion of configuration to yield the enantiomeric tertiary alcohol. This reactivity is in stark contrast to carbenoids derived from alkyl carbamates, which trapped both boronic esters and trialkyl boranes with retention of configuration.[39] In the case of secondary benzylic carbamates, mesomeric stabilization of the anion into the aromatic ring causes the sp^3 centre to become partly planarized, which results in the build-up of electron density on the opposite face of the lithium ion.[47,48] When a carbenoid was quenched with a boronic ester, it was proposed that an oxygen atom of the boronic ester coordinated to the lithium ion of the carbenoid prior to nucleophilic attack, which resulted in formation of a boronate complex with retention of stereochemistry. In the case of

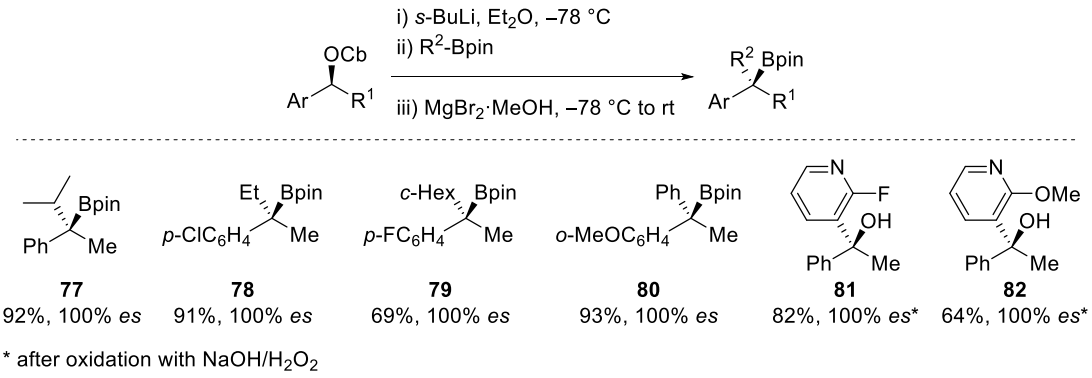
boranes, no such coordination is possible and the trialkyl borane approacheed from the bottom face of the carbenoid, which is less hindered and has sufficient electron density, resulting in inversion of configuration at the sp^3 centre. Through judicious choice of organoboron species it was therefore possible to obtain either enantiomer of tertiary alcohol from the same enantioenriched secondary alcohol (Scheme 22). Primary boronic ester and trialkyl borane derivatives were well tolerated, with ethyl boronic ester and triethyl borane giving tertiary alcohols **73** and **ent-73** in 95% and 91% yield, respectively, and both with complete—but opposite—enantiospecificity. The more sterically hindered isopropyl boron derivatives both gave the respective products **74** and **ent-74** in high yield; however, a slight erosion of the enantiomeric ratio was observed for both the alcohol derived from the boronic ester (**74**, 96:4 *er*) and the borane (**ent-74**, 2:98 *er*). Incorporating electron deficient aryl groups also yielded products with a reduced enantiomeric ratio value, as exemplified by examples **75** and **ent-75**. Phenyl substituted boranes could not be used as the products decomposed through a protodeboronation pathway during the oxidation phase; however, phenyl boronic esters were competent substrates, as demonstrated by alcohol **76**, which was obtained in 89% yield and with 96:4 *er* (Scheme 22).



Scheme 22 Enantiodivergnt synthesis of tertiary alcohols

The erosion of enantiomeric excess occurred when the reaction was warmed to ambient temperature to facilitate 1,2-migration of the boronate complex.[40] Upon warming, the boronate complex underwent reversible fragmentation and reformed the stabilized benzylic carbenoid and boronic ester. Partial racemization of the carbenoid occurred at elevated temperature before recombination with the boronic ester yielded a boronate complex of undesired configuration, which underwent subsequent 1,2-migration to

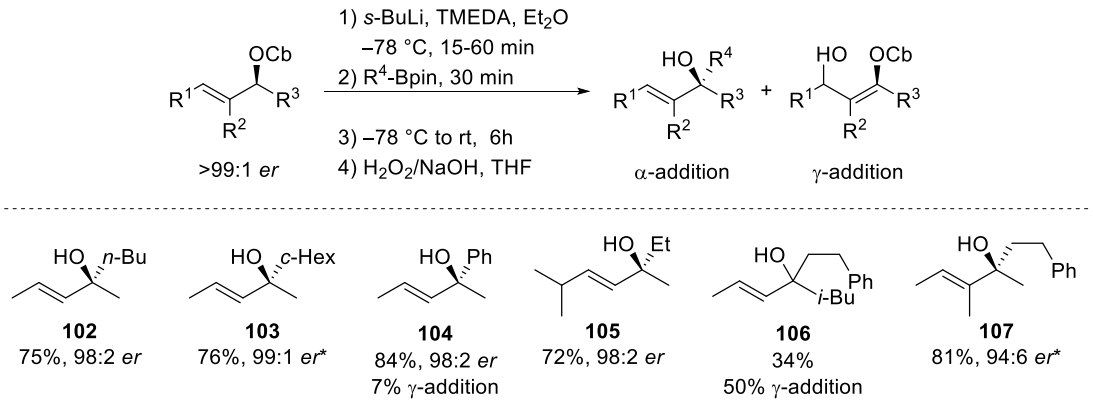
generate the tertiary alcohol of undesired configuration. As discussed previously, complete enantiospecificity could be restored through addition of $MgBr_2$·MeOH prior to warming the reaction mixture to permit 1,2-migration. Under these conditions a wide range of electron rich, electron deficient and sterically hindered tertiary boronic esters were synthesized in high yield and with perfect enantiospecificity; notable examples being substrates **77**, **78**, and **79**, which were obtained with diminished enantiomeric ratio values in the absence of $MgBr_2$·MeOH. The reaction also tolerated pyridyl boronic esters,[44] which generated α-pyridyl tertiary alcohols **81** and **82** after oxidation with $NaOH/H_2O_2$ (Scheme 23).



Scheme 23 Complete enantiospecificity in the synthesis of tertiary boronic esters

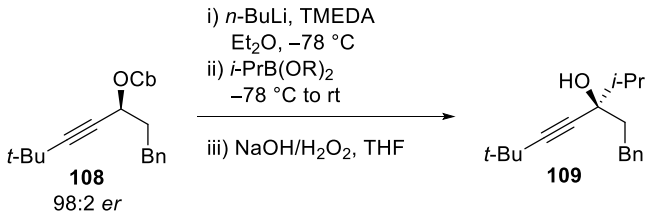
The synthesis of tertiary allylic boronic esters was achieved through lithiation–borylation reactions with suitable enantioenriched allylic carbamates.[41] Hoppe has shown that treatment of lithiated secondary allylic carbamates with electrophiles such as Me_3SnCl or methyl chloroformate leads to a mixture of products derived from α- and γ-attack of the organolithium,[45] while aldehydes react through a Zimmerman–Traxler type transition state to yield γ-substituted products.[46] Boronic esters primarily undergo α-attack of the organolithium due to coordination of a pinacol oxygen atom to the lithium (Scheme *24*).[41] Primary and secondary boronic esters yielded products of α-addition exclusively, with **102** being obtained in 75% yield and 98:2 *er* and **103** being obtained in 76% yield and 99:1 *er* following the addition of $MgBr_2$·MeOH at –78 ºC. In the case of secondary boronic esters, lower enantiomeric ratio values were obtained in the absence of $MgBr_2$·MeOH, as the hindered boronate complex reversibly regenerated the stabilized allylic lithiated species, which partially racemized and recombined with the boronic ester. The reaction tolerated aryl boronic esters; however, small amounts of γ-addition were observed, with product **104** obtained in 84% yield and with 98:2 *er* together with 7% of the γ-addition product. The α/γ-ratio in the products was also influenced by the

substituents on the carbamate. Increasing the steric bulk at the γ-position reinforced the regioselectivity for borylation at the α-position, with alcohol **105** being obtained exclusively as the α-addition product. Conversely, increasing the steric bulk at the α-position resulted in increased formation of γ-addition products, as exemplified by substrate **106**. Increasing the steric bulk of the R^2 position of the carbamate did not result in the formation of γ-addition products but did contribute to a reduction in the enantiospecificity of the reaction, with compound **107** being obtained in 94:6 *er* with the addition of $MgBr_2$·MeOH following the formation of boronate complex (Scheme 24).



Scheme 24 Synthesis of tertiary allylic alcohols

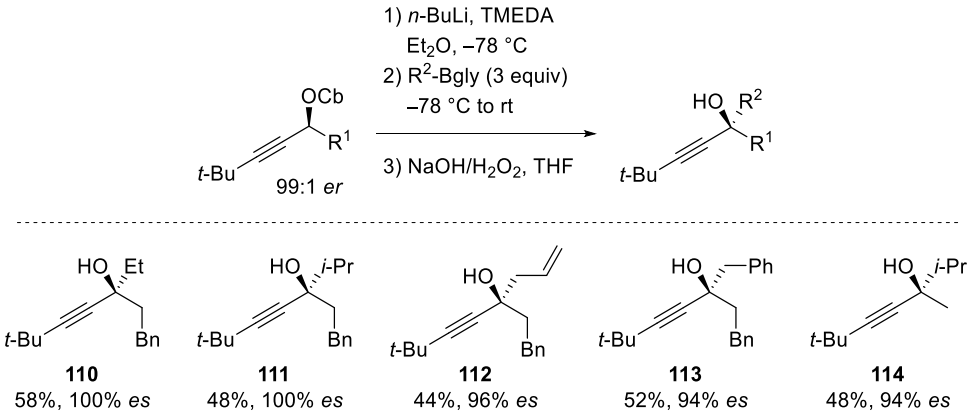
The synthesis of tertiary propargylic alcohols was achieved through lithiation–borylation reactions with suitable enantioenriched propargylic carbamates.[42] Hoppe has shown that lithiated propargylic carbamates are only configurationally stable at –78 °C when there is a bulky substituent in the terminal position of the alkyne,[47] and so the scope of the reaction was limited to *t*-butyl substituted alkynes. Propargylic carbamate **108** was lithiated with *n*-BuLi and the resulting carbenoid quenched with isopropyl pinacolato boronic ester, which yielded propargylic alcohol **109** after oxidation with no regiomeric products from γ-addition to the alkyne; however, **109** was racemic (Scheme 25, entry 1). The enantiospecificity of the reaction was improved by using the less sterically hindered neopentyl boronic ester, with **109** being obtained in 38% *es* when using two equivalents of the boronic ester (Scheme 25, entry 3). A further increase in the enantiospecificity was observed when using three equivalents of boronic ester (81% *es*, Scheme 25, entry 4); however, utilization of isopropyl ethylene glycolato boronic ester resulted in the formation of **109** with complete enantiospecificity (Scheme 25, entry 5).



Entry	Diol	Boronic ester (equiv)	Yield (%)	*es* (%)
1	Pinacol	2	55	2
2	Pinacol	3	55	4
3	Neopentyl	2	51	38
4	Neopentyl	3	80	81
5	Ethylene glycol	2	48	100

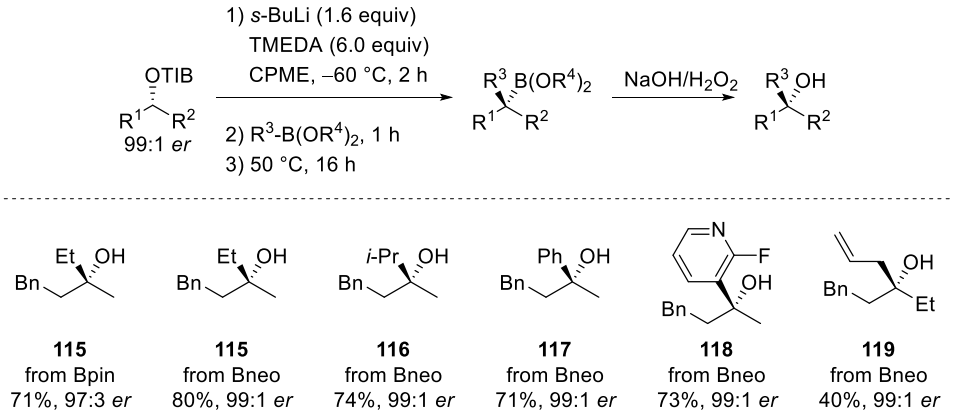
Scheme 25 Effect of boronic ester ligand on enantiospecificity in the homologation of secondary propargylic carbamates

The dependence of the *es* value on both the equivalents of the boronic ester used and on the boronic ester ligand suggests that the erosion in enantioenrichment is caused by reversibility of the boronate complex, racemization of the carbenoid upon warming and recombination with the boronic ester. In the case of hindered pinacolato boronic esters reversibility is much faster than 1,2-rearrangement, which results in the complete fragmentation of the boronate complex and isolation of a racemic alcohol. The boronate complex derived from a neopentyl boronic ester is less hindered and so less prone to reversible fragmentation, while increasing the number of equivalents of the boronic ester increases the likelihood that the carbenoid will recombine with the boronic ester before extensive racemization occurs. Ethylene glycol boronic esters are less hindered than neopentyl boronic esters and promote 1,2-migration over reversibility, permitting the isolation of propargylic alcohols with high to perfect enantiospecificity. Under the optimized conditions primary, secondary, allylic and benzylic boronic esters all participated in the reaction to yield propargylic alcohols **110**, **111**, **112**, and **113**, respectively, with high levels of enantiospecificity (Scheme *26*). Phenyl boronic ester also participated in the reaction, but the tertiary alcohol could not be isolated as the corresponding boronic ester underwent facile protodeboronation before oxidation.



Scheme 26 Synthesis of tertiary propargylic alcohols

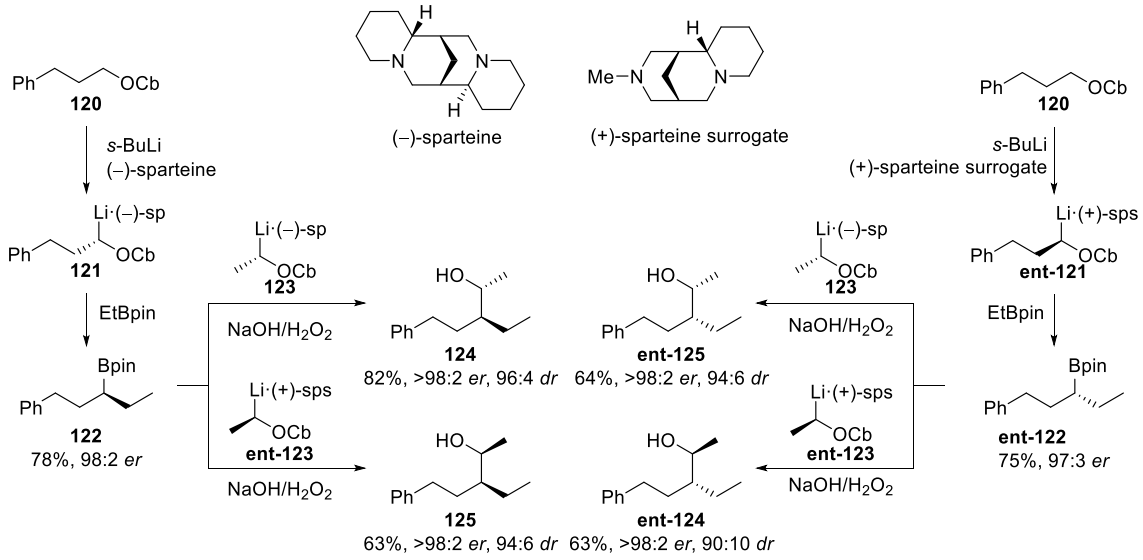
The generation of tertiary trialkyl boronic esters using lithiation–borylation methodology is challenging because secondary dialkylbenzoates[48] and carbamates[49] are normally resistant to deprotonation. Despite this, Aggarwal has shown that stereospecific lithiation of secondary dialkylbenzoates can be achieved under modified conditions:[43] treatment of a secondary dialkylbenzoate with *s*-BuLi/TMEDA (1.6/6.0 equiv) in CPME at –60 ºC for 2 h, which resulted in up to 90% lithiation. Quenching the lithiated species derived from 4-phenylbutan-2-yl benzoate with ethyl pinacolato boronic ester, followed by oxidation, generated alcohol **115** in 71% yield and 97:3 *er*; however, utilizing the less hindered neopentyl boronic gave **115** in 80% yield and with complete enantiospecificity (Scheme 27). Using these conditions secondary (**116**), aryl (**117** and **118**) and allylic (**119**) boronic esters were tolerated. Increasing the steric bulk of the starting benzoate gave the desired products (**119**) but in lower yield because of the more challenging lithiation (Scheme 27).



Scheme 27 Synthesis of tertiary alcohols from secondary dialkyl benzoates

Assembly–Line Synthesis

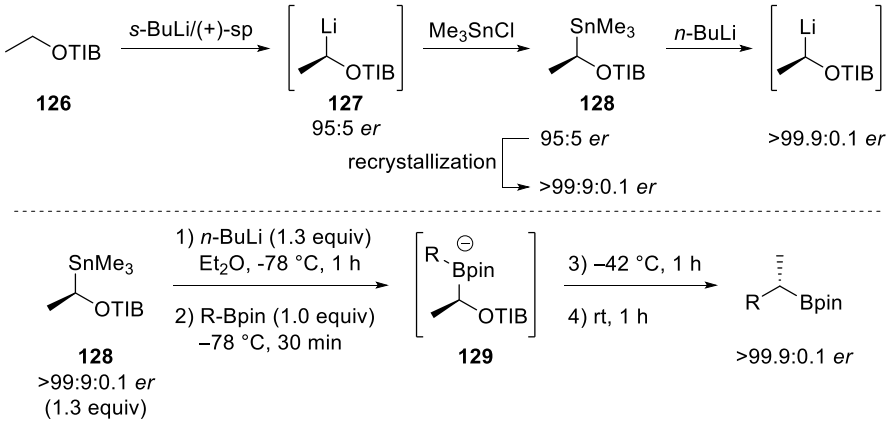
Aggarwal has shown that the homologation of boronic esters using lithiated carbamates can be performed iteratively to generate complex molecules with exquisite control of stereochemistry.[50] In this vein, all four diastereoisomers of alcohol **124** were prepared through two sequential homologations of carbamate **120** by varying the enantiomer of chiral reagent used in each step (Scheme 28).[50] The lithiation of carbamate **120** with *s*-BuLi and (–)-sparteine yielded lithiated species **121**, which was quenched with ethyl boronic ester to afford secondary boronic ester **122** in 78% yield and 98:2 *er* after 1,2-metallate rearrangement. The enantiomeric ratio corresponds to the selectivity of the lithiation step, which is faithfully transferred through the enantiospecific formation of the boronate complex and subsequent 1,2-migration. Homologation of **122** with (–)-sparteine ligated carbenoid **123** and oxidation gave secondary alcohol **124** in 96:4 *dr* and >98:2 *er*. The diastereoisomer (**125**) was obtained by homologating **122** with (+)-sparteine surrogate coordinated carbenoid **ent-123**, again with high diastereo- (94:6 *dr*) and enantiomeric ratios (>98:2 *er*). The use of the O'Brien (+)-sparteine surrogate[51] was required due to the commercial unavailability of (+)-sparteine at the time. **Ent-124** and **ent-125**, were obtained with high enantiomeric ratio values and with 94:6 *dr* and 9:1 *dr*, respectively, through homologation with the opposite enantiomer of chiral reagents at each step, thus showing that each step is operating under reagent control (Scheme 28).



Scheme 28 Synthesis of all four stereoisomers of alcohol **124**

In 2014, the Aggarwal group published the synthesis of a molecule containing 10 contiguous methyl substituted stereogenic centres with complete stereocontrol via the

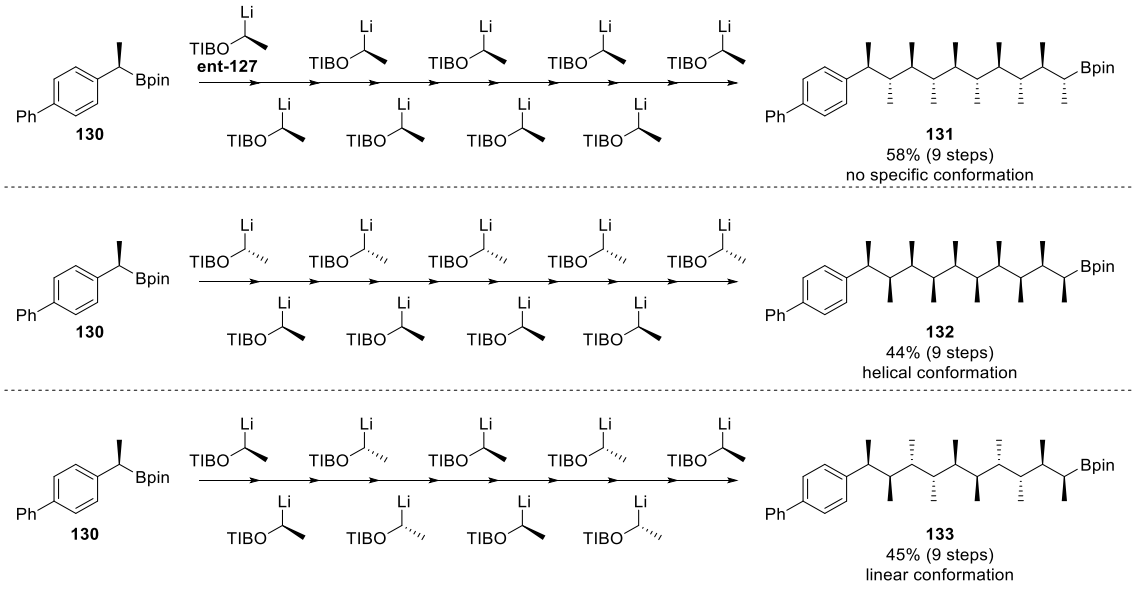
homologation of boronic esters.[52] This feat is particularly impressive as both the diastereoselectivity and the amount of over- and under-homologation must be controlled. For example, if each homologation proceeded to 98% completion, with 1% over-homologation and 1% under-homologation, after 10 homologation steps the desired product would be only 82% pure. If each homologation proceeded in 98:2 *er*, the final product would again only be 82% pure after 10 homologations, with the mass balance being made up with diastereoisomers that could prove difficult to separate. Controlling the enantioselectivity of each step is particularly challenging because the lithiation of ethyl benzoate **126** with a combination of *s*-BuLi and (+) or (–)-sparteine provides lithiated species **127** in only 95:5 *er*. This was overcome by synthesizing α-stannyl benzoate **128**, which could be recrystallized to >99.9:0.1 *er*. Stereospecific tin–lithium exchange was achieved through the addition of *n*-BuLi to stannane **128** to obtain carbenoid **127** with retention of configuration and as a single enantiomer (Scheme 29).[52]



Scheme 29 Homologation of a boronic ester with enantiopure carbenoid **127**

128 was used in excess with respect to the boronic ester to ensure complete conversion to boronate complex **129** and thus prevent under-homologation. To prevent over-homologation, the excess carbenoid was decomposed at –40 °C for one hour before the reaction mixture was warmed to ambient temperature to facilitate 1,2-migration. The reaction mixture was then filtered to remove the insoluble LiOTIB salt and concentrated to yield the homologated boronic ester for use in the next iteration. Although seven homologations could be performed without any additional purification steps, the authors elected to perform an aqueous work up after every third homologation. With the optimized homologation conditions in hand, the authors synthesized the all-anti diastereoisomer **131** by subjecting boronic ester **130** to nine iterative homologations with lithiated species **ent-127**. **131** was obtained as a single enantiomer and diastereoisomer.

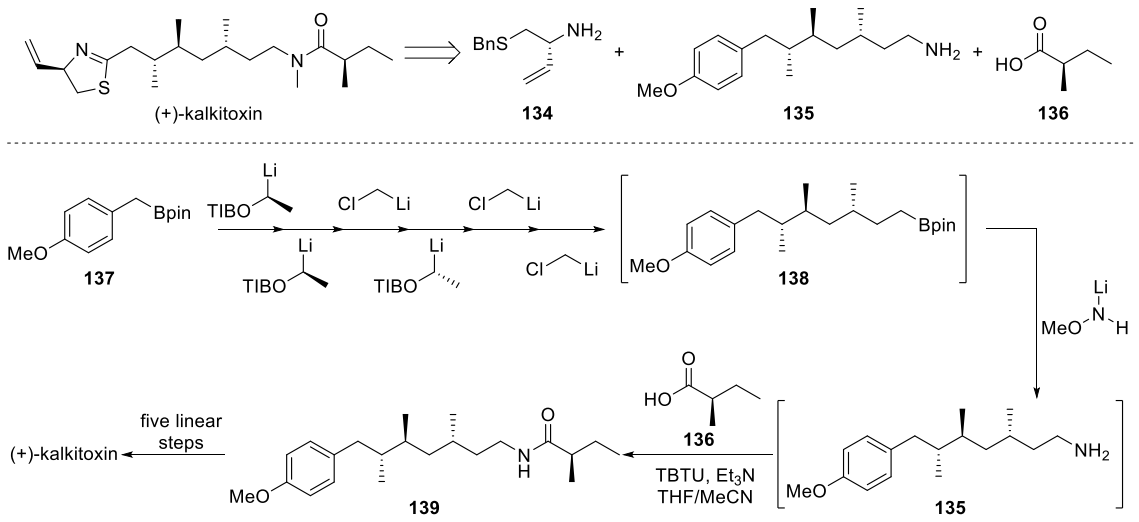
This sequence was repeated to generate the all-syn diastereoisomer **132** by altering the enantiomer of lithiated species used in each homologation, and the syn–anti diastereoisomer **133** was synthesized by alternating the enantiomer of lithiated species in every other homologation. Poly-methyl substituted alkyl chains often adopt specific conformations to avoid syn-pentane interactions along the chain. Although the all-*anti* diastereoisomer **131** exhibited no conformational preference, the all-syn diastereoisomer **132** adopted a helical conformation and the syn–anti diastereoisomer **133** adopted a linear conformation (Scheme 30).



Scheme 30 Assembly-line synthesis of molecules **131**, **132**, and **133**

As a further demonstration of the power of Aggarwal's assembly-line synthesis, the natural products (+)-kalkitoxin and (+)-hydroxyphthioceranic acid were synthesized with exceptional efficiency and stereocontrol.[53] (+)-Kalkitoxin was assembled from fragments **134**, **135**, and **136**. The synthesis of fragment **135** could be further simplified to PMB-substituted boronic ester **137** through an assembly-line sequence using the requisite stannane-derived lithiated benzoate or (chloromethyl)lithium and subsequent amination of boronic ester **138**. In the event, homologated boronic ester **138** was achieved following six assembly–line manipulations. The only purification that was required between each homologation was a simple filtration to remove LiOTIB. The conversion of boronic ester **138** to amine **135** proceeded as described by Morken and coworkers,[54] and was followed by an aqueous extraction and an amide coupling with fragment **136**, which furnished amide **139** in 52% yield from boronic ester **137**, and with >95:5 *dr* and >99:1 *er*. Remarkably, the entire sequence took only four days and required only one purification

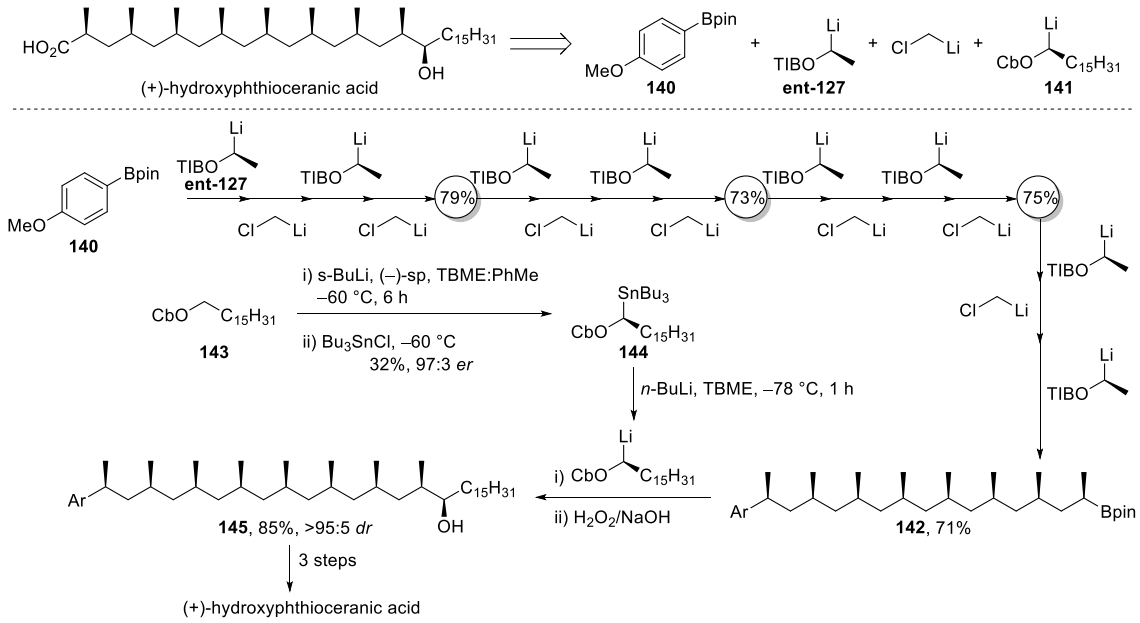
step! The completion of the synthesis was achieved in a further five linear steps (Scheme 31).



Scheme 31 Synthesis of (+)-kalkitoxin

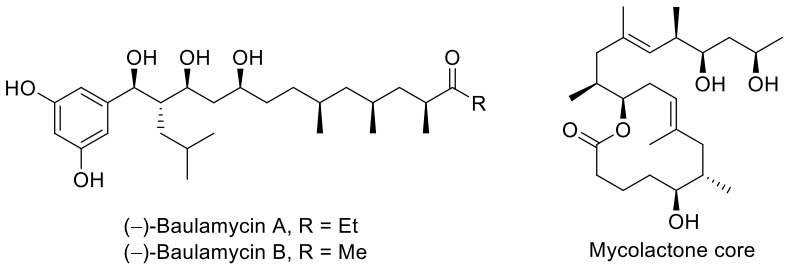
(+)-Hydroxyphthioceranic acid is a component of sulfolipid-1, which itself is a constituent of the cell wall of *Mycobacterium tuberculosis*.[55] Retrosynthetic analysis of (+)-hydroxyphthioceranic acid revealed aryl boronic ester **140** as a suitable starting point for synthesis by alternating homologations with lithiated benzoate **ent-127** and (chloromethyl)lithium followed by a final homologation with lithiated carbamate **141** and oxidative cleavage of the PMP group. This synthetic route required sixteen iterative homologation reactions. Upon launching the assembly-line sequence, it was found that adventitious impurities limited the efficiency of the process, and so column chromatography was performed after every fourth homologation. Under these conditions, boronic ester **142** was achieved after fifteen homologation reactions and only four chromatographic purifications. Homologation of **142** with carbamate **143** was impeded by the insolubility of the carbamate in Et_2O and TBME at –78 °C, which prevented lithiation. Hoppe has shown that to achieve lithiation in a related substrate, an excess of *s*-BuLi and (–)-sparteine (4.0 equiv) was required.[56] Such an excess of *s*-BuLi is inappropriate in this case as it would form an irreversible boronate complex with the boronic ester and significantly reduce the yield. Instead, stannane **144** was prepared in 32% yield by lithiating **143** in a mixture of TBME and PhMe at –60 °C. **144** showed improved solubility in TMBE, and the lithiated species was liberated through the addition of an equimolar quantity of *n*-BuLi. Fragment **145** was obtained in 85% yield and >95:5 *dr* after oxidation with basic hydrogen peroxide. Ruthenium catalysed oxidative

removal of the PMP group completed the synthesis. Impressively, the entire synthesis was achieved in only one month and with a total of seven purification steps (Scheme 32).



Scheme 32 Synthesis of (+)-hydroxyphthioceranic acid

Assembly-line synthesis has been applied to the synthesis of additional natural products, such as (–)-baulamycin A and B[57] and the mycolactone core[58] (Scheme 33). The modularity of assembly-line synthesis was an essential feature in the synthesis of (–)-baulamycin A and B as the authors were required to synthesize several diastereisomers to determine the correct structure.[57]



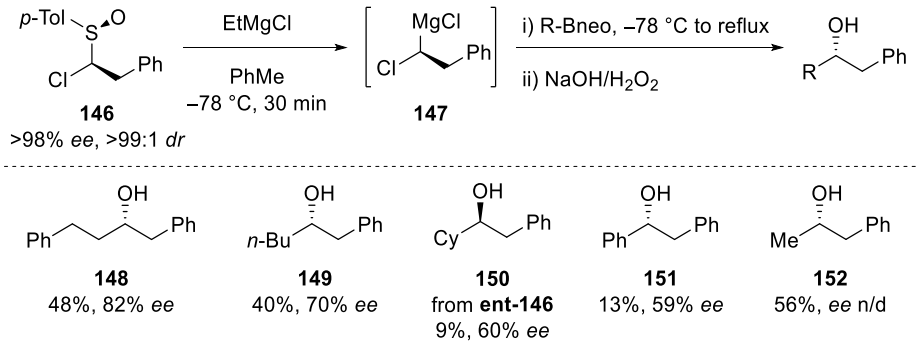
Scheme 33 Baulamycins A and B and the mycolactone core

Sulfoxides as Carbenoid Precursors

Homologation of boronic esters with carbenoids derived from α-chlorosulfoxides

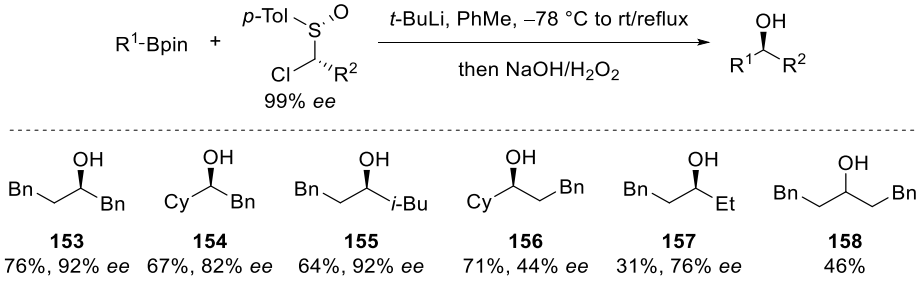
Blakemore has shown that reagent-controlled homologation of boronic esters can also be achieved using α-chloro organolithium/Grignard reagents, which can be derived in enantioenriched form from the corresponding enantiopure Hoffmann α chlorosulfoxides[59] by sulfoxide–metal exchange.[60] Treatment of α-chlorosulfoxide **146**

with EtMgCl generated the corresponding magnesium carbenoid (**147**), which after addition of a boronic ester and heating to reflux gave the homologated boronic ester which was subsequently oxidised. Using this approach, alcohols **148**–**152** were obtained; however, the enantiomeric ratio values were not synthetically useful (Scheme 34). The low *er* values are presumably due to partial racemization of the carbenoid prior to boronate complex formation.



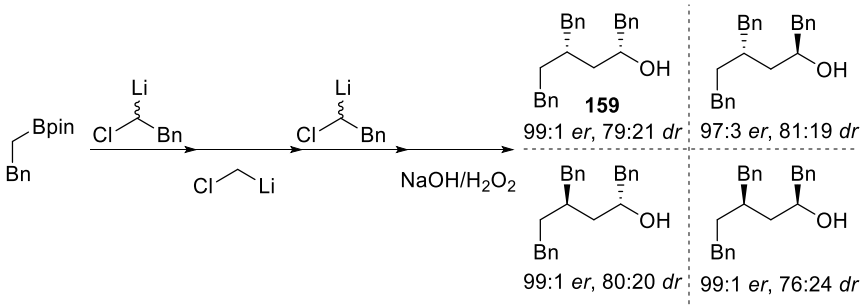
Scheme 34 Homologation of boronic esters using magnesium carbenoids derived from the corresponding α-chloro sulfoxide by sulfoxide–magnesium exchange

α-Chloro lithium carbenoids can be generated by addition of *t*-BuLi, to α-chlorosulfoxides. In contrast to the corresponding magnesium carbenoids, α-chloro lithiated species are chemically unstable and must be liberated in the presence of a boronic ester (*in situ* lithiation) to prevent decomposition.[61] Under these conditions, sulfoxide–lithium exchange is faster than direct addition of butyllithium to the boronic ester; moreover, the formation of a boronate complex is faster than decomposition of the carbenoid. The lithium carbenoid was superior to the magnesium carbenoid in terms of both yield and enantiospecificity and could accommodate the use of pinacolato boronic esters. Primary and secondary pinacolato boronic esters participated and gave **153** and **154**, respectively, in good yield but with slightly reduced enantiomeric excess values (92% and 82% *ee*, respectively). While the alcohol derived from isobutyl sulfoxide (**155**) was obtained with good levels of enantiospecificity, generally, modification of the sulfoxide component resulted in much lower enantiomeric excess values, as shown by example **157** (Scheme 35).



Scheme 35 Homologation of boronic esters using lithium carbenoids derived from the corresponding α-chloro sulfoxide by sulfoxide–lithium exchange

Blakemore sought to showcase this methodology through the synthesis of all four stereoisomers of alcohol **159**, which were constructed through a three-step iterative sequence of homologations followed by terminal oxidation.[61] In each case the desired alcohol was obtained with an excellent enantiomeric ratio value; however, the diastereomeric ratio values were comparatively low. The low diastereoselectivity values are caused by a chiral amplification phenomenon, whereby the minor enantiomer from the first homologation is transferred into a different diastereomeric series in the second homologation.[62] This process is a limitation of iterative reagent-controlled homologation processes that do not use enantiopure reagents (Scheme 36).

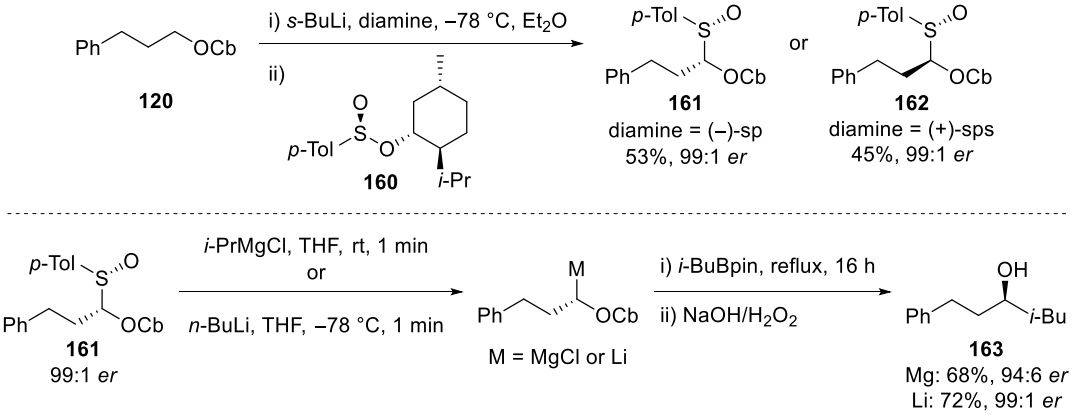


Scheme 36 Synthesis of all four diastereoisomers of alcohol **159**

Homologation of boronic esters with carbenoids derived from α-sulfinyl carbamates

O'Brien reported the synthesis of α-sulfinyl carbamates as precursors to α-metallated carbamates and showed their application to boron homologation reactions with a single example utilizing isobutyl pinacolato boronic ester.[63] The synthesis of either enantiomer of α-sulfinyl carbamate **161** was achieved in 99:1 *er* through asymmetric lithiation of the parent carbamate **120** and subsequent trapping with Andersen's chiral sulfonate[64] (**160**). The high enantiomeric ratio value observed in the synthesis of **161** was general to all α sulfinyl carbamates synthesised in this way, as the minor enantiomer after lithiation was delivered into a different diastereomeric series upon trapping with sulfonate **160** and was removed during purification. Transmetallation of sulfoxide **161** with *i*-PrMgCl or *n*-BuLi

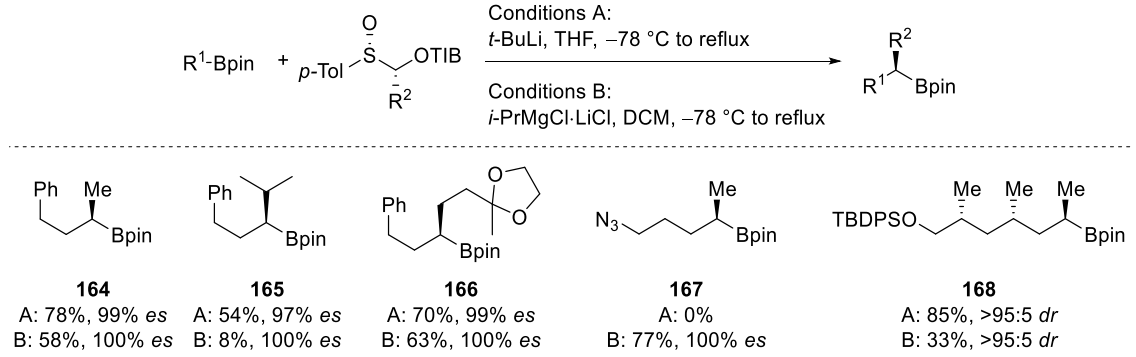
revealed the magnesium or lithium carbenoid, respectively, which were quenched with isobutyl pinacolato boronic ester. Both the magnesium and lithium carbenoids afforded alcohol **163** in high yield; however, the lithium carbenoid proved superior in terms of enantiospecificity and generated **163** without erosion of enantiomeric ratio (Scheme 37).



Scheme 37 Homologation of *i*-BuBpin with carbenoids derived from α-sulfinyl carbamate **161**

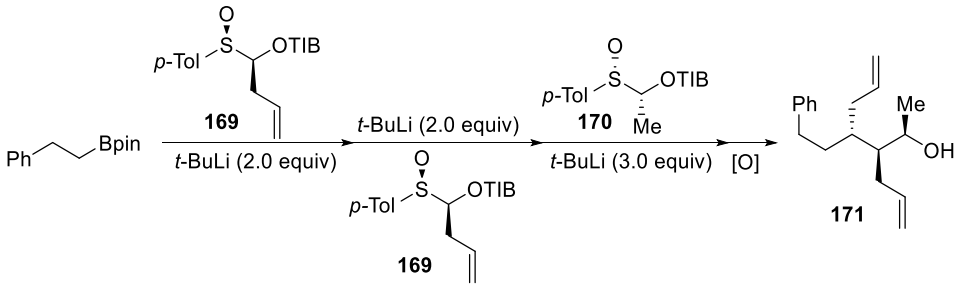
Homologation of boronic esters with carbenoids derived from α-sulfinyl benzoates

The utility of α-sulfinyl benzoates as precursors to α-lithiated benzoates was investigated by Aggarwal as an alternative to α-stannyl benzoates.[65] In contrast to α-stannyl benzoates, α-sulfinyl benzoates are generally non-toxic and are obtained in >99:1 *er* without recrystallization, which permits the use of non-crystalline α-sulfinyl benzoates as carbenoid precursors. Metallation of an α-sulfinyl benzoate with *t*-BuLi (conditions A) or *i*-PrMgCl·LiCl[66] (conditions B**)** liberated the lithium or magnesium carbenoid, respectively, which was quenched with a boronic ester. α-Sulfinyl benzoates containing primary alkyl groups performed well under both sets of conditions, as shown by boronic ester **164**, which was isolated in excellent yield and enantiospecificity. Similarly, the α-sulfinyl benzoate substituted with an isopropyl group underwent the homologation reaction to yield boronic ester **165** with exquisite enantiospecificity; however, when using the magnesium carbenoid the yield was poor due to the enhanced steric demand of the substrate. Some common functional groups that are incompatible with lithiation chemistry, for example, azides, could be tolerated when using a magnesium carbenoid, as shown in example **167**. Finally, the reaction showed complete reagent-control, as demonstrated by substrate **168**, which was obtained in >95:5 *dr* when using either the lithium or magnesium carbenoid; however, steric demand again resulted in a low yield in the case of the magnesium carbenoid (Scheme 38).



Scheme 38 Homologation of boronic esters with carbenoids derived from α-sulfinyl benzoates

Having demonstrated the feasibility of using α-sulfinyl benzoates as carbenoid precursors in boron homologation reactions, Aggarwal reported the synthesis of contiguously substituted alcohol **171** through an iterative sequence with outstanding control of selectivity; however, the efficiency of the reaction diminished with increasing steric demand.[65] Whilst the first two homologation reactions with allylic α-sulfinyl benzoate **169** proceeded with almost complete conversion of starting material to product, the third homologation utilizing methyl α-sulfinyl benzoate **170** required an extra equivalent of *t*-BuLi (3.0 equiv instead of 2.0 equiv) to achieve 85% conversion, which highlights the threshold at which steric hindrance inhibits homologation with α-sulfinyl benzoate derived lithiated carbenoids. After oxidation, alcohol **171** was achieved in 41% overall yield and with >95:5 *dr*, demonstrating that high diastereoselectivity can be achieved in an iterative process as long as the carbenoid is enantiopure and the reaction is entirely stereospecific (Scheme *39*).



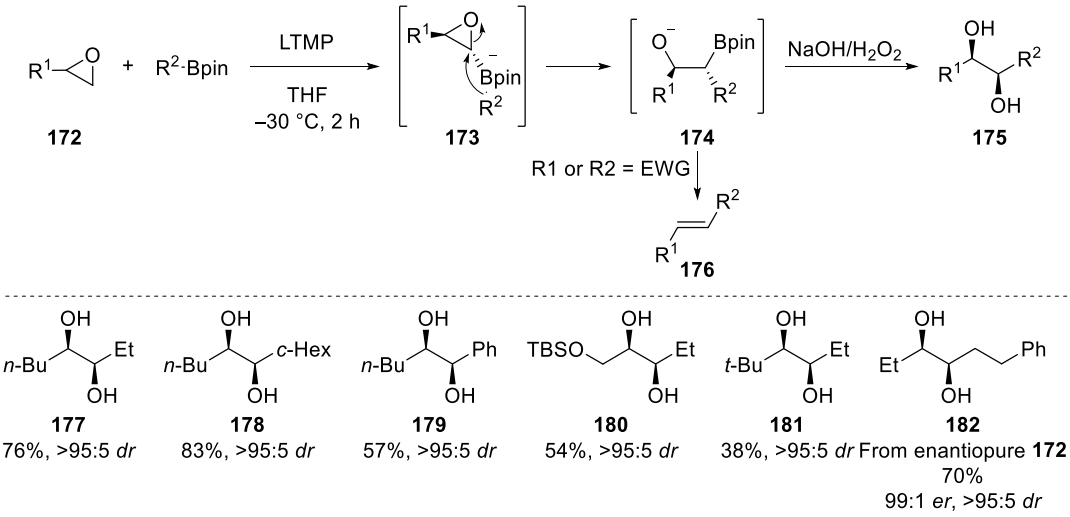
1st P:SM	2nd P:SM	3rd P:SM	Yield (%)	*dr*
98:2	96:4	85:15	41	>95:5

Scheme 39 Aggarwal's iterative synthesis of alcohol **171**

Homologation of Boronic Esters with Cyclic Carbenoids

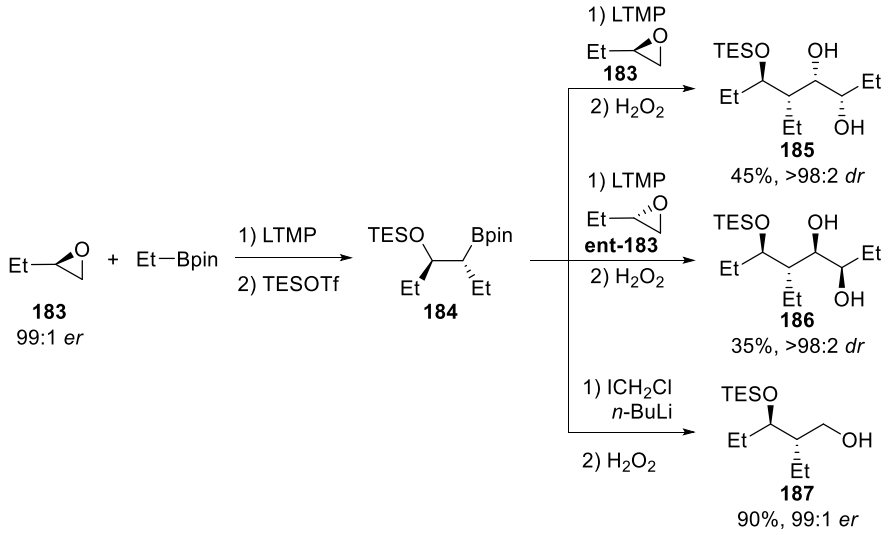
Homologation of boronic esters with lithiated epoxides

Aggarwal has shown that enantioenriched 1,2-diols can be obtained by the reaction of boronic esters with lithiated epoxides.[67] Treatment of terminal epoxide **172** with LTMP in the presence of a boronic ester (*in situ* lithiation) generated the trans lithiated epoxide exclusively, which was immediately quenched by the boronic ester to yield boronate complex **173.** Stereospecific 1,2-metallate rearrangement then gave β-hydroxy boronic ester **174**, which was oxidized to the corresponding syn 1,2-diol as a single diastereoisomer (Scheme 40). The success of the reaction was influenced by the electronics of both the epoxide and the boronic ester. Electron donating groups promoted formation of the desired product, whereas electron withdrawing groups promoted decomposition of intermediate α-hydroxy boronic ester **174** through a boron-Wittig type elimination to yield an alkene, such as **176**. Primary and secondary alkyl boronic esters were well tolerated, for example, diols **177** and **178** were obtained in high yield and as single diastereoisomers. Incorporation of groups with an intermediate electronic profile, such as aryl groups, resulted in a reduced yield of the product due to the competing elimination pathway; however, syn-diol **179** was still obtained in good yield and as a single diastereoisomer. Employing sterically hindered and heteroatom containing epoxides delivered **180** and **181** in moderate yields and with perfect diastereocontrol. Finally, when an enantioenriched epoxide was used, the desired 1,2-diol was obtained with complete enantiospecificity, as shown by example **182**.



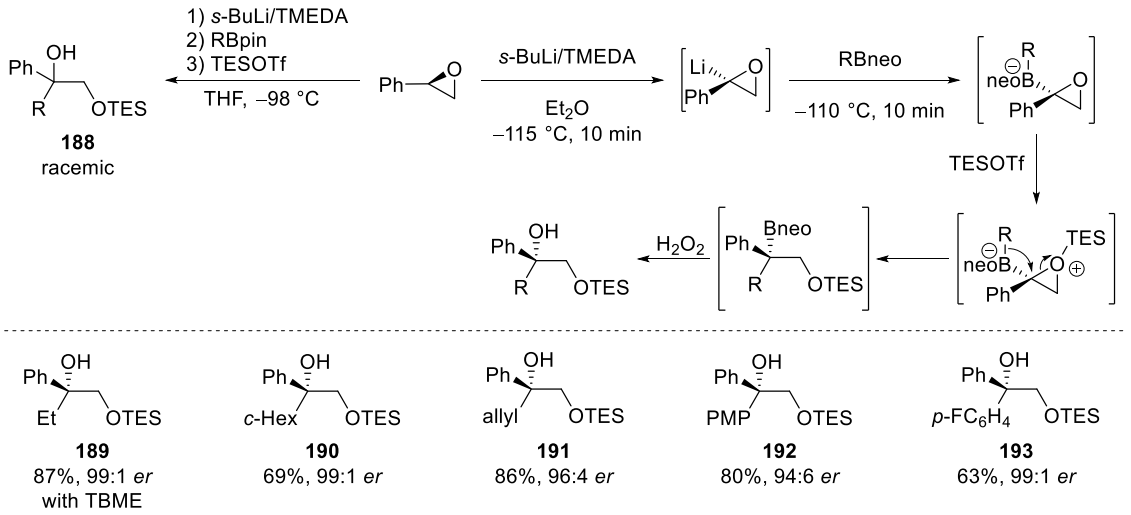
Scheme 40 Homologation of boronic esters with lithiated epoxides

Further elaboration of intermediate β-hydroxy boronic ester **174** was also possible. Specifically, the addition of TESOTf after boronate complex formation generated protected β-hydroxyl boronic ester **184**, which was re-subjected to the reaction conditions. Treatment of **184** and either enantiomer of epoxide **183** with LTMP furnished diastereomeric triols **185** and **186**, each in good yield and with perfect diastereoselectivity. Other transformations of boronic ester **184** were also applied. A one-carbon homologation reaction yielded 1,3-diol **187** with an excellent enantiomeric ratio value (Scheme 41).



Scheme 41 Elaboration of boronic ester **184**

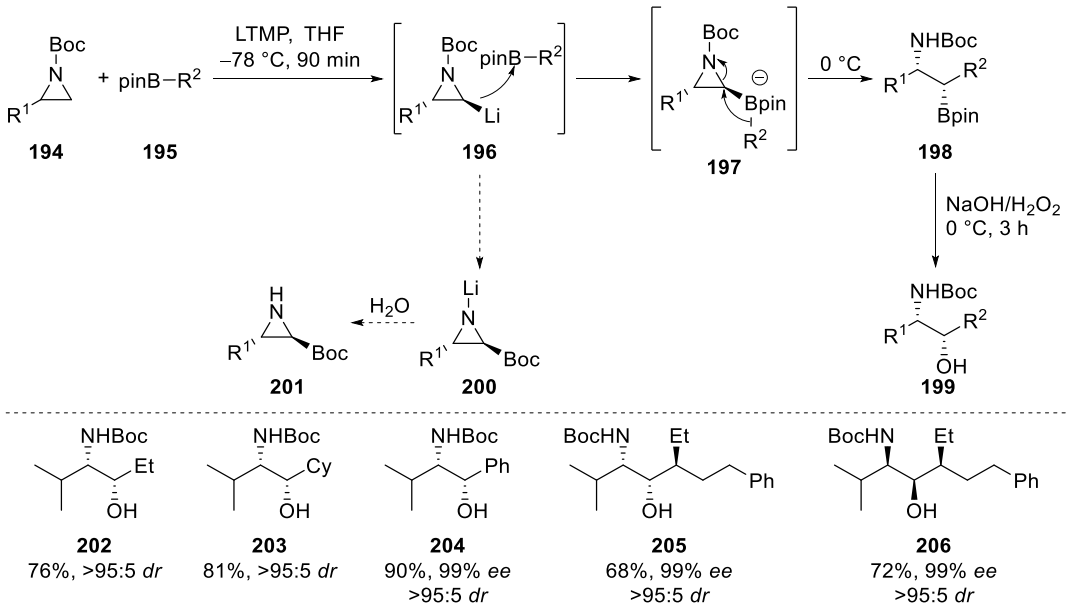
Florio has shown that styrene oxide can be regiospecifically lithiated at the benzylic position by the addition of *s*-BuLi and TMEDA at –98 ºC. The lithiated species was then trapped with electrophiles with retention of stereochemistry and perfect enantiospecificity.[68] However, when a boronic ester was employed and TESOTf was added after boronate complex formation, Aggarwal obtained tertiary alcohol **188** as a racemate.[67] The enantiospecificity of the reaction could be improved by reducing the reaction temperature from –98 to –115 °C and by utilizing the less hindered neopentylglycol boronic ester derivatives. Under these conditions, primary and secondary alkyl boronic esters performed well, yielding tertiary alcohols **189** and **190** in 87% and 69% yield respectively and with 99:1 *er*. The reaction tolerated boronic esters containing both electron rich and electron poor arenes, as exemplified by substrates **192** and **193** (Scheme 42).[67]



Scheme 42 Homologation of boronic esters with styrene oxide

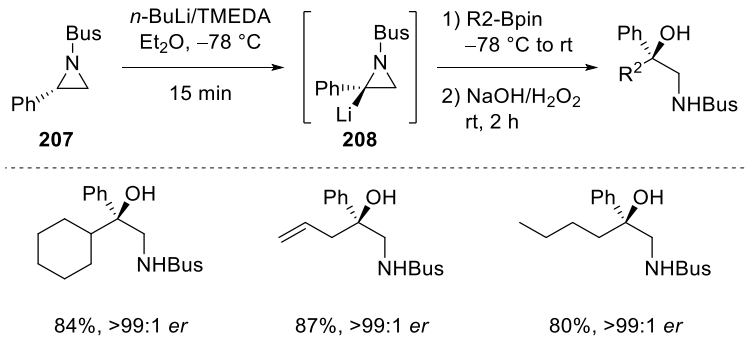
Homologation of boronic esters with lithiated aziridines

The formation of 1,2-amino alcohols can be achieved through the reaction of a lithiated *N*-protected aziridine with a boronic ester.[69] Specifically, trans-lithiation of *N*-Boc protected aziridine **194** with LTMP in the presence of boronic ester **195** generated boronate complex **197**, which underwent 1,2-metallate rearrangement to yield syn-1,2-amino alcohol **199** after oxidation of the boronic ester with basic peroxide.[69] Hodgson has shown that when lithiated aziridine **196** is generated in the absence of a suitable electrophile, Boc-group migration occurs to form aziridinyl esters, such as **201**, after aqueous work up.[127,128] To supress this potential side reaction, the reaction was performed at the highest reasonable concentration (0.5 M) and with an excess of the boronic ester (3.0 equiv). Under these conditions, the desired 1,2-amino alcohols were obtained exclusively with complete suppression of the side reaction (Scheme 43). Primary and secondary boronic esters were well tolerated, with amino alcohols **202** and **203** obtained with complete diastereoselectivity and in 75% and 81% yield, respectively, when starting from the racemic aziridine. Utilizing an enantiopure aziridine permitted the formation of amino alcohols with complete enantio- and diastereocontrol, as shown by example **204**. In addition, employing an enantioenriched boronic ester gave diastereoisomers **205** and **206** with complete enantio- and diastereocontrol, thus showing that the process operated under complete reagent control (Scheme 43).



Scheme 43 Homologation of boronic esters with lithiated aziridines

Florio has shown that lithiation at the benzylic position of 2-phenyl-*N*-Boc-aziridine with *s*-BuLi results in the exclusive migration of the Boc-group through an aza-Wittig type [1,2] rearrangement.[72] Aggarwal subsequently found that migration of the *N*-protecting group could be prevented by employing the less labile *N*-Bus protecting group.[69] Specifically, treatment of 2-phenyl-*N*-Bus-aziridine with n-BuLi/TMEDA gave lithiated species **208**, which was quenched with a boronic ester to yield amino alcohols bearing quaternary stereogenic centres after oxidation (Scheme *44*).

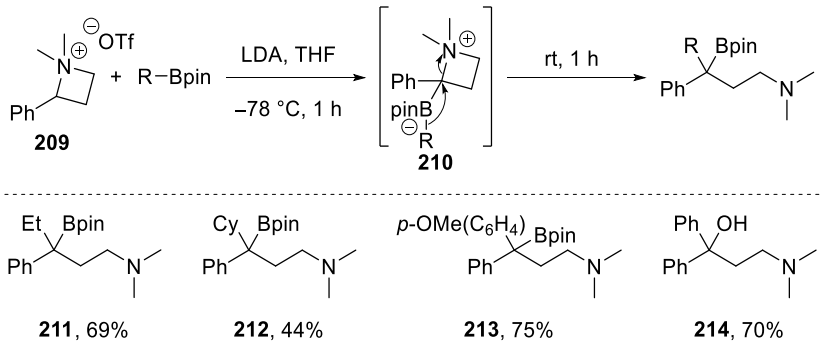


Scheme 44 Homologation of boronic esters with aziridine **207**

Homologation of boronic esters with lithiated azetidinium ions

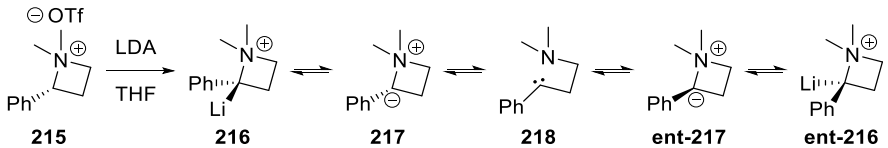
The synthesis of γ-amino boronic esters through lithiation–borylation reactions is challenging as α-aryl *N*-Boc azetidines are resistant to deprotonation; however, the corresponding azetidinium ions can be deprotonated at the benzylic position with lithium amide bases.[73] The resulting organolithium—a lithium stabilized carbanion/ylide—is chemically unstable and accordingly must be generated in the presence of a boronic ester

to ensure trapping before decomposition. Aggarwal has shown that treatment of azetidinium **209** and a boronic ester with LDA at –78 ˚C in THF formed boronate complex **210**, which underwent 1,2-migration upon warming to room temperature to generate the desired tertiary γ-dimethylamino boronic ester (Scheme 45).[73] The reaction tolerated primary and secondary alkyl boronic esters, as exemplified by **211** and **212**, which were isolated in 69% and 44% yield, respectively. Electron rich aryl boronic esters also performed well, with *para*-methoxyphenyl boronic ester yielding product **213** in 75% yield; however, when more electron poor aryl groups were used, such as phenyl boronic ester, the tertiary boronic ester derivatives could not be isolated due to protodeboronation of the products. Despite this, tertiary alcohol derivative **214** could be isolated in 70% yield after an oxidative work up with $NaOH/H_2O_2$ (Scheme 45).



Scheme 45 Homologation of boronic esters with lithiated azetidinium ions

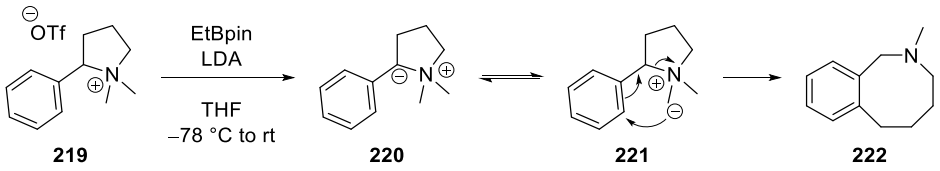
Employing enantioenriched azetidinium ion **215** did not lead to the formation of enantioenriched products, due to the configurational instability of lithiated species **216**. It was shown that the lithium stabilized carbanion is in equilibrium with the corresponding ylide **217**, which underwent racemization through carbene intermediate **218**, thus generating racemic products (Scheme 46).[73]



Scheme 46 Mechanism of lithiated azetidinium ion racemization

The process was not expandable to five-membered pyrrolidinium **219**, which instead underwent Sommelet–Hauser rearrangement to yield benzo-fused 1,2,3,4,5,8-hexahydroazocine **222** as the only product (Scheme 47).[73] The exclusive formation of **222** suggested that either; (i) formation of the boronate complex is much slower than the putative rearrangement, or (ii) 1,2-metallate rearrangement of the

boronate complex is slow, so the boronate complex instead reverts to the starting boronic ester and stabilized carbanion. The origin of the slow migration can be attributed to the decreased ring strain in pyrrolidinium **219** when compared to azetidinium **209** (Scheme 47).

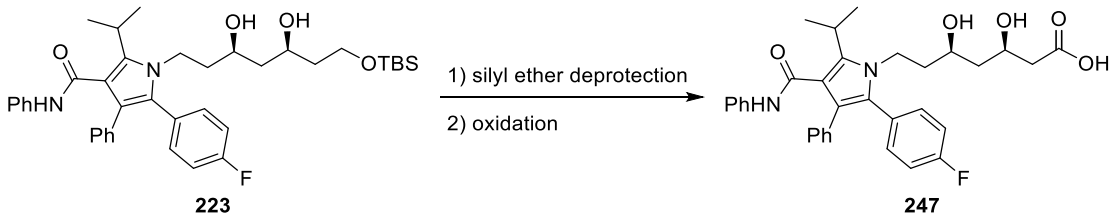


Scheme 47 Sommelet–Hauser rearrangement of pyrrolidinium **219**

Chapter 1: Synthesis of Atorvastatin Derivative 223

Project aim

It had been shown within our group that diborylmethane (**225**) can be used as linchpin reagent in the synthesis of 1,2- and 1,3-bis(boronic esters) through lithiation–borylation reactions with sparteine ligated or diamine free carbenoids, respectively (Scheme 49).[74] To further showcase this methodology we aimed to demonstrate a concise synthesis of compound **223**, a derivative of the blockbuster statin, atorvastatin (**247**), by combining the reactivity of sparteine ligated and diamine-free carbenoids with diborylmethane (Scheme 48). Compound **223** could be transformed into atorvastatin (**247**) through deprotection of the silyl ether and subsequent oxidation of the primary alcohol.



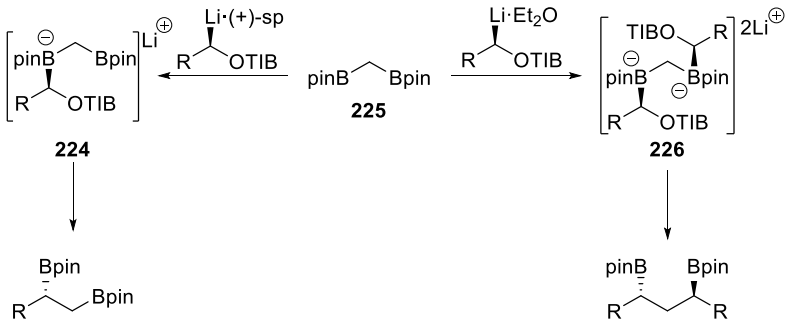
223 **247**

Scheme 48 Transformation of compound **223** into atorvastatin (**247**)

Introduction

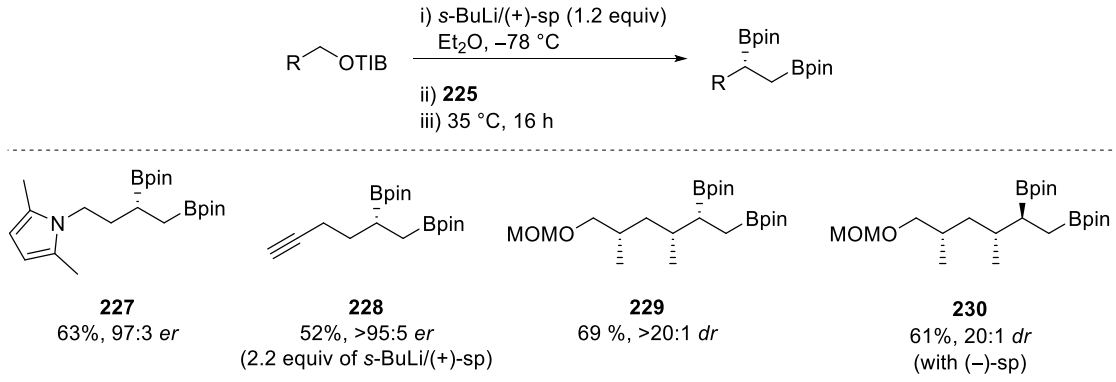
Homologations of diborylmethane

Diborylmethane (**225**) can act as a linchpin reagent in the synthesis of 1,2- and 1,3-bis(boronic esters),[74] where the product obtained is dependent on the nature of the carbenoid employed. In the case of (+) or (–)-sparteine ligated carbenoids, diborylmethane was homologated at one boronic ester to afford 1,2-bis(boronic esters). Formation of single boronate complex **224** was facile; however, the carbenoid was too hindered to generate a further boronate complex with the remaining boronic ester within the same molecule. Conversely, diamine-free carbenoids are unhindered and can homologate diborylmethane (**225**) twice to afford symmetrical 1,3-bis(boronic esters). In this instance, the carbenoid formed bis(boronate complex) **226**—from reaction at both boronic esters in **225**—which both underwent 1,2-metallate rearrangement (Scheme 49).



Scheme 49 Single and double homologation of diborylmethane (**225**) with lithiated benzoates

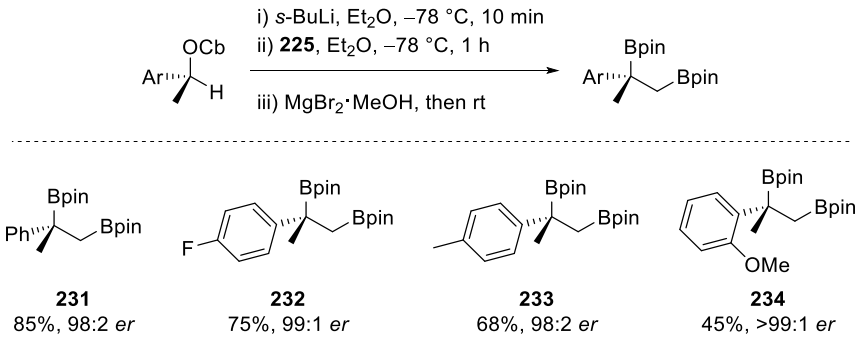
The synthesis of a range of enantioenriched 1,2-bis(boronic esters) was achieved through homologation of diborylmethane (**225**) with primary benzoates. The reaction tolerated nitrogen functionality when protected as a pyrrole group, as exemplified by product **227**, which was isolated in 63% yield and with 97:3 *er*. The scope of the reaction extended to a broad range of substrates, including several that are challenging to make using current transition metal catalysed diboration methods,[91,92] for example, substrates containing alkynes or proximal stereogenic centres. Substrates containing terminal alkynes were tolerated when the alkyne was protected *in situ* as its conjugate base through addition of an additional equivalent of *s*-BuLi and (+)-sparteine, as shown by product **228**. The reaction operated under reagent control, as exemplified by products **229** and **230**, which were both isolated in good yields and with excellent diastereomeric ratios (Scheme 50).



Scheme 50 Synthesis of 1,2-bis(boronic esters) through the reaction of diborylmethane (**225**) with primary benzoates

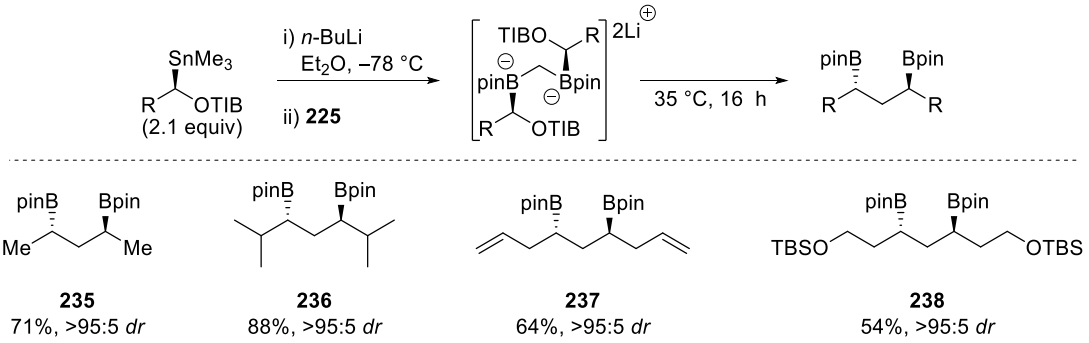
The synthesis of primary–tertiary 1,2-bis(boronic esters) through the diboration of 1,1-disubstituted alkenes does not proceed in useful yield or enantioselectivity;[75] however, homologation of diborylmethane (**225**) with lithiated secondary benzylic carbamates provided primary–tertiary 1,2-bis(boronic esters) **231**–**234** with complete control of enantioselectivity. The reaction was insensitive to the electronic nature of the aromatic rings and tolerated electron rich and electron poor substrates. *o*-Substituted

aromatics were also tolerated, albeit with a reduced yield, but with no reduction in enantiomeric ratio (Scheme 51).



Scheme 51 Synthesis of 1,2-bis(boronic esters) through the reaction of diborylmethane (**225**) with secondary benzylic carbamates

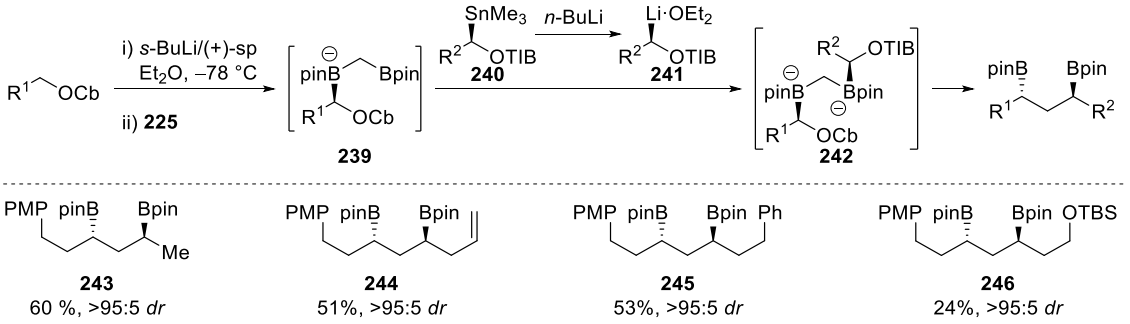
The synthesis of symmetrical 1,3-bis(boronic esters) was achieved in one operation through the addition of diborylmethane (**225**) to an excess of diamine-free carbenoid, generated from the corresponding α-stannyl benzoate through stereospecific tin–lithium exchange using *n*-BuLi. Primary and secondary alkyl carbenoids participated in the reaction, as shown by products **235** and **236**, which were both isolated in high yield and with excellent diastereomeric ratios. Carbenoids containing alkenes and silyl ethers were also well tolerated, yielding products **237** and **238** with high stereoselectivity (Scheme 52).



Scheme 52 Synthesis of symmetrical 1,3-bis(boronic esters) using diborylmethane (225) as linchpin reagent

The synthesis of non-symmetrical 1,3-bis(boronic esters) was also achieved in a one-pot procedure from diborylmethane (**255**). Specifically, after formation of mono(boronate complex) **239** by reaction of **225** with 1 equiv of sparteine-ligated carbenoid, stannane **240** was added to the reaction mixture. *In situ* formation of carbenoid **241** was achieved through addition of *n*-BuLi, which reacted with **239** to give bis(boronate complex) **242**. Subsequent 1,2-metallate rearrangement of both boronate complexes afforded

non-symmetrical 1,2-bis(boronic esters) **243** to **246**, each with perfect diastereocontrol (Scheme 53).



Scheme 53 Synthesis of non-symmetrical 1,3-bis(boronic esters) using diborylmethane (**225**) as linchpin reagent

Atorvastatin

As a further display of the utility of this reaction, we aimed to synthesise a derivative of atorvastatin (**247**), which is marketed by Pfizer under the brand name Lipitor (Figure 1). Atorvastatin is one of the most commercially successful drug ever developed, earning Pfizer $12.7 billion in 2007 alone. Lipitor came off patent in 2011, allowing a host of generic versions to enter the market.

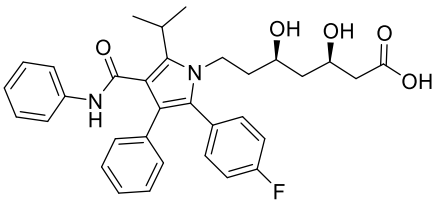
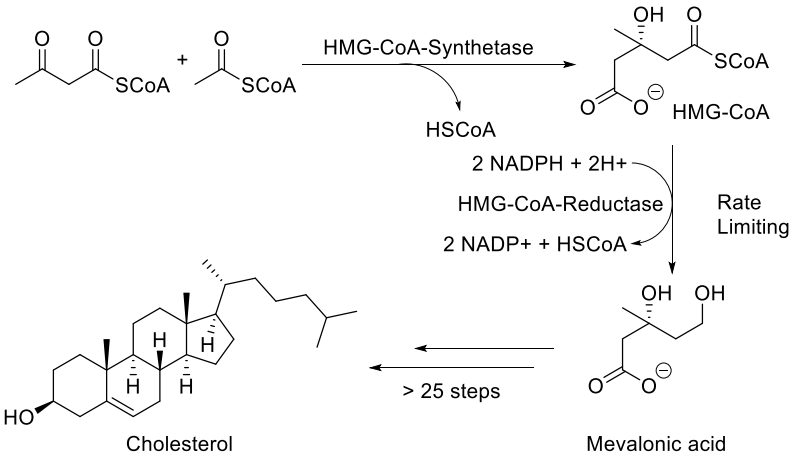


Figure 1 Atorvastatin (**247**)

Like all statins, atorvastatin is an inhibitor of HMG-CoA-reductase, which is the enzyme responsible for the reduction of HMG-CoA to mevalonic acid in the early stages of cholesterol biosynthesis (Figure 2). Lipitor is a competitive inhibitor of HMG-CoA but does not inhibit binding of the cofactor, NADPH. The protein exists as a tetramer with each of the neighbouring monomers contributing to the structure of the active site. The binding mode of a number of statins was elucidated in 2001 by Deisenhofer[77] who solved the crystal structure of the catalytic portion of HMG-CoA-reductase bound to various statins (Figure 2). Atorvastatin shares common structural motifs with HMG-CoA and mevalonic acid and does indeed bind the enzyme in the same way. The terminal carboxylate forms an interaction with Lys^{735}, while the hydroxyl groups bind to Ser^{684}, Asp^{690}, Lys^{691}, Lys^{692}, Glu^{559} and Asp^{767}. As mevalonic acid is released from the active

site it can be assumed that not all the interactions are stabilizing. Atorvastatin therefore has additional interactions, through a hydrogen bond from its amide to Ser^{565}, as well as Van Der Waals interactions with residues Leu^{562}, Val^{683}, Leu^{853}, Ala^{856} and Leu^{857}. The combination of these interactions leads to atorvastatin having an IC_{50} value of 8nM.[77]



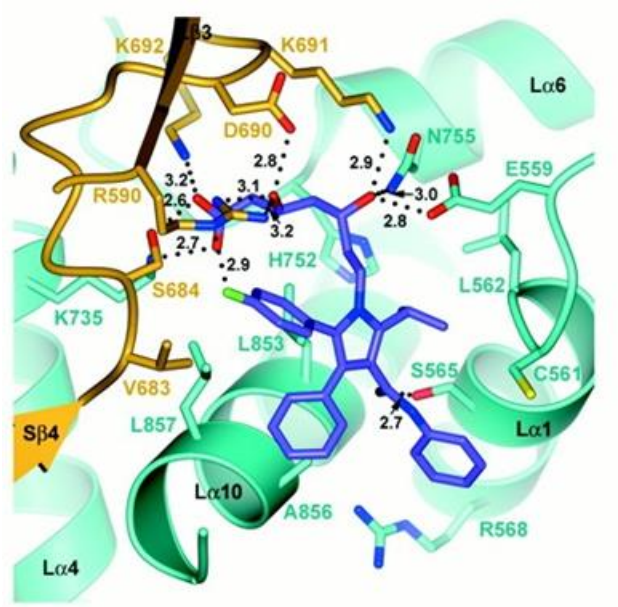
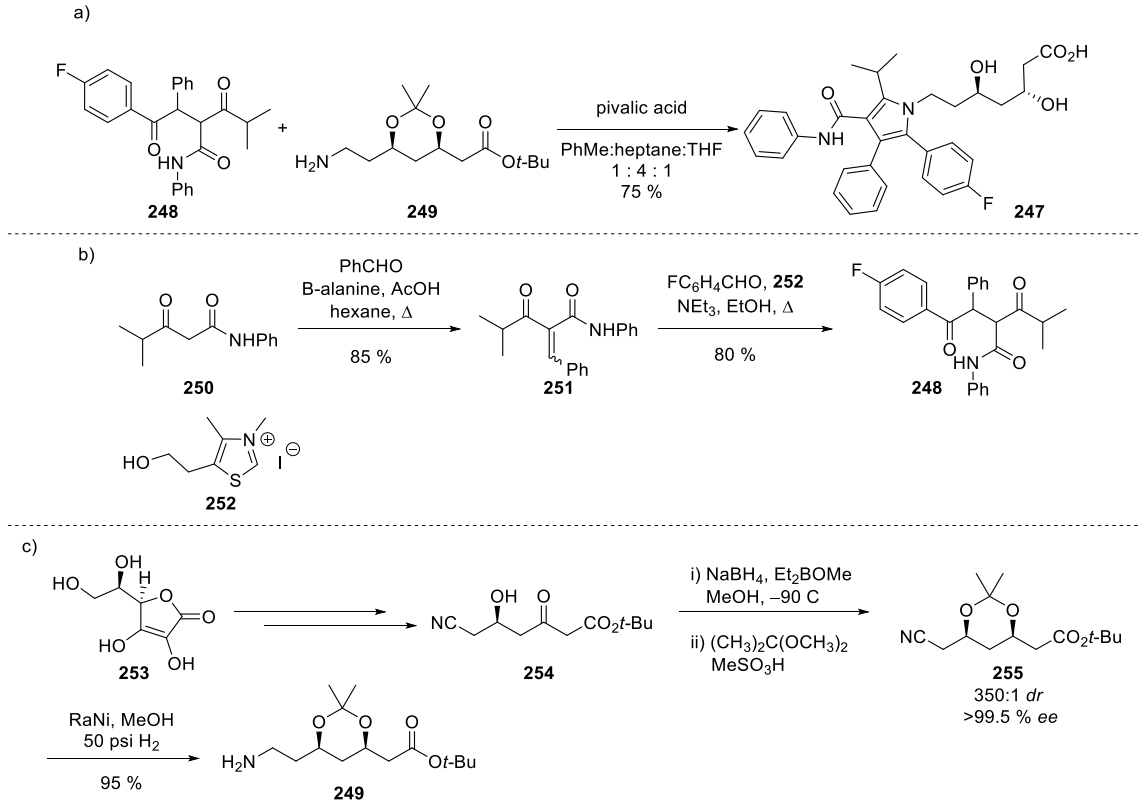


Figure 2 Binding mode of atorvastatin

Industrial Synthesis of Atorvastatin

The industrial synthesis of atorvastatin was achieved by the coupling of the fragments **248** and **249** in a highly optimised Paal−Knorr reaction (Scheme 54a) using a catalytic amount of pivalic acid followed by deprotection of the acetonide and t-butyl ester.[78] Fragment **248** was made in two steps from diketone **250**, initially by condensation with benzaldehyde to afford intermediate **251**. An umpolung 1,4-addition of parafluorobenzaldehyde was then achieved through a Stetter reaction to yield the desired diketone **248** in 64% yield over two steps (Scheme 54b). The asymmetric synthesis of

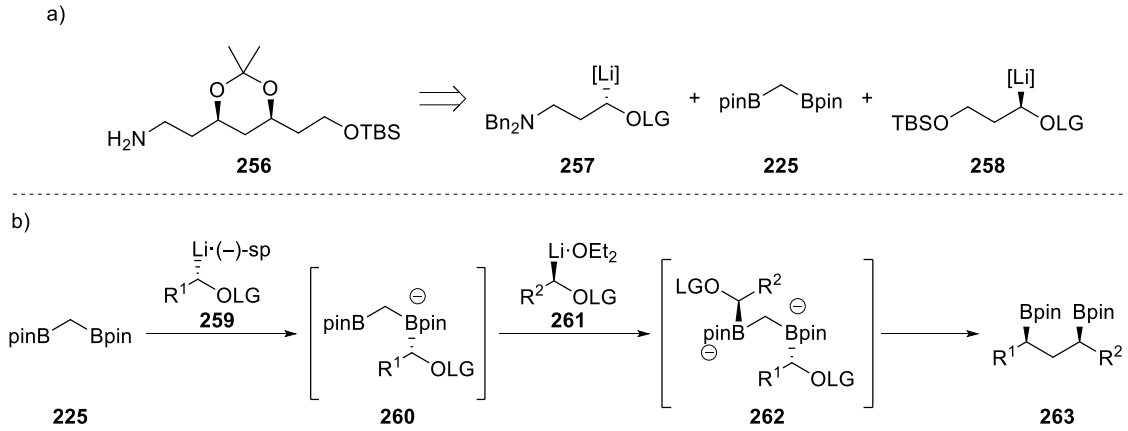
fragment **249** was achieved in from isoascorbic acid (**253**) in high yield and diastereoselectivity (Scheme 54c).[79] A number of functional group interconversions led to advanced fragment **254**. *Syn*-selective reduction of the ketone was performed according to a procedure described by Narasaka,[80] followed by acetonide protection, which generated intermediate **255**. Finally, the primary amine was revealed through high-pressure hydrogenation of the nitrile to afford unprotected fragment **249**.



Scheme 54 The industrial synthesis of atorvastatin

Choice of Target and Retrosynthetic Analysis

We decided that synthesis of acetonide protected amine **256**, which differs from fragment **249** only by carboxylic acid protecting group, would constitute a fragment that could easily be transformed into atorvastatin (**247**). The synthesis of **256** would proceed through a one pot, bidirectional, desymmetrising lithiation−borylation reaction between diborylmethane (**225**) and carbenoids **257** and **258**. (Scheme 55a). This one-pot process would be achieved by mono addition of (–)-sparteine-ligated carbenoid **259** to diborylmethane (**225**) to generate boronate complex **260**. Formation of diamine-free carbenoid **261** in the presence of **260** would form the second boronate complex (**262**), which after 1,2-metallate rearrangement would afford the desired 1,3-diboronic ester (**263**), which would be oxidised and protected (Scheme 55b).



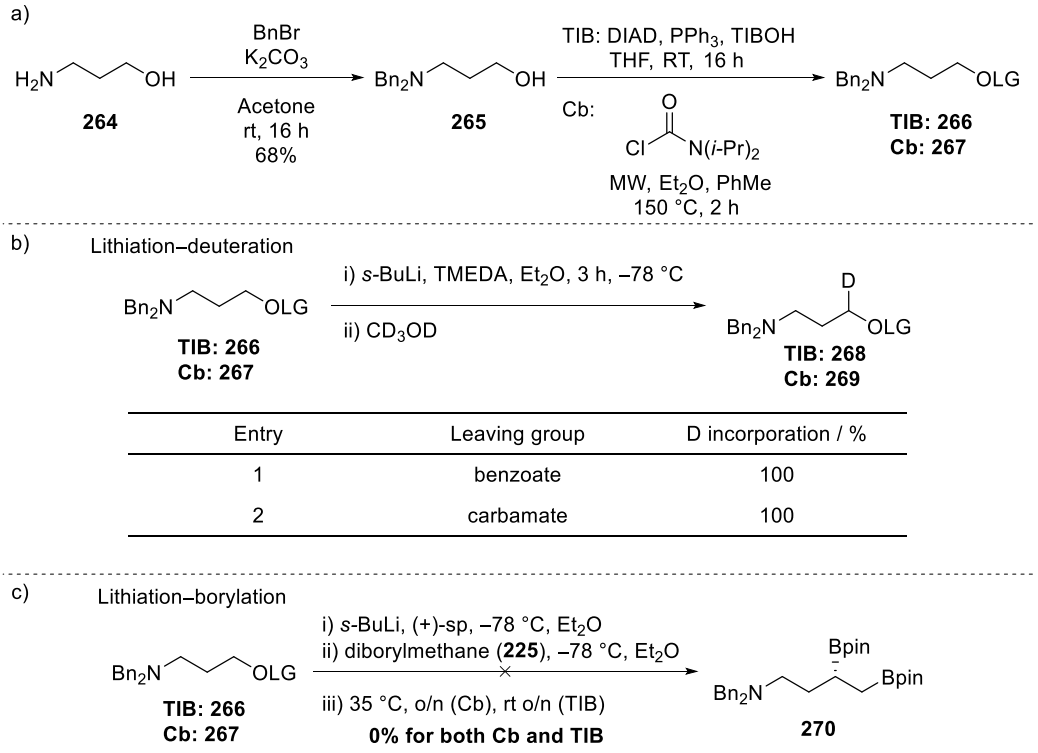
Scheme 55 Retrosynthetic analysis of **256**

Results and Discussion

Selecting the optimal leaving group

Before attempting this transformation it was necessary to determine which leaving group would prove superior, and so both benzoate **268** and carbamate **267** of 3-dibenzylaminopropanol (**264**) were prepared (Scheme 56a). Amine **264** was bis(protected) with benzyl bromide in reasonable yield to afford amine **265**, which was converted into benzoate **266** under Mitsunobu conditions, and carbamate **267** by reaction with *N*,*N*-diisopropylcarbamoyl chloride. The lithiation of both benzoate **266** and carbamate **267** was then evaluated in a lithiation−deuteration study by deprotonation with *s*-BuLi in the presence of TMEDA followed by quenching with deuterated methanol (Scheme 56b). Gratifyingly, both benzoate **266** and carbamate **267** displayed full deuterium incorporation when quenched with CD_3OD after a lithiation period of 3 h, as determined by ^1H NMR analysis. With this positive result the diboration of carbenoid precursors **266** and **267** with diborylmethane (**225**) was attempted (Scheme 56c). **266** and **267** were lithiated with *s*-BuLi and (+)-sp for a period of 3 h. Diborylmethane (**225**) was added and the resulting mixture stirred at −78 °C for 1 h. The benzoate was then stirred overnight at room temperature to permit 1,2-migration, whereas the carbamate was heated at 35 °C for the same period. Disappointingly, no product was obtained under these conditions for either the benzoate or the carbamate. As lithiation has been proven to occur, this result must either be due to inefficient boronate complex formation, the formation of a reversible boronate complex that decomposes upon warming to diborylmethane (**225**) and the respective carbenoid or slow 1,2-migration. ^{11}B NMR analysis of the reaction mixture after the borylation phase showed that formation of a boronate complex was not

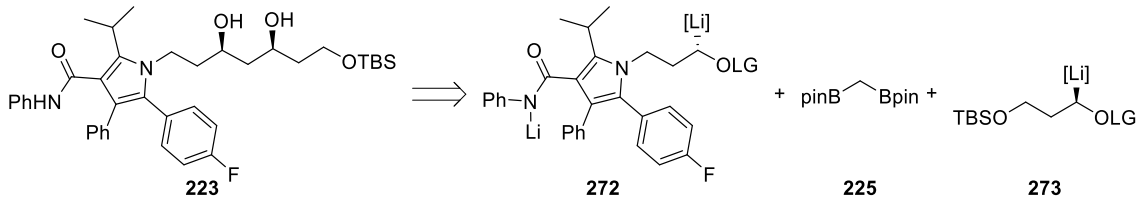
occurring, which may be due to stabilisation of the carbenoid by coordination of the nitrogen atom lone pair to the lithium ion, thus reducing its nucleophilicity.



Entry	Leaving group	D incorporation / %
1	benzoate	100
2	carbamate	100

Scheme 56 Evaluation of leaving group in the lithiation–borylation reaction of **266** and **267** with **225**

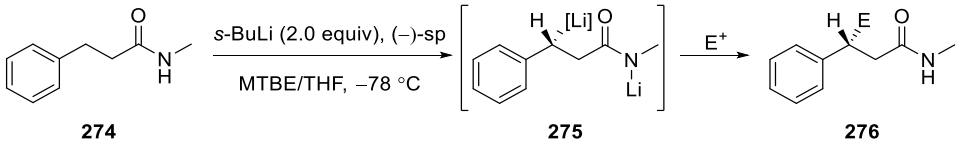
As a result, we sought an alternative protecting group where the nitrogen lone pair is not available for donation. On evaluation of our target, we decided that a pyrrole would be perfectly suited to this role as the nitrogen lone pair would be implicated in the aromaticity of the ring and would allow us to alter our target to compound **223**, which includes the substituted pyrrole of atorvastatin (Scheme 57).



Scheme 57 Retrosynthetic analysis of **223**

The presence of an acidic amide proton added a complication to our proposed key step; however, there is literature precedence for performing lithiation reactions in the presence of unprotected amides when using an excess of *s*-BuLi to protect the amide *in situ* as its conjugate base (Scheme 58). Beak has shown that benzylic lithiation can be achieved in the presence of an unprotected amide by addition of an additional equivalent of *s*-BuLi.[81]

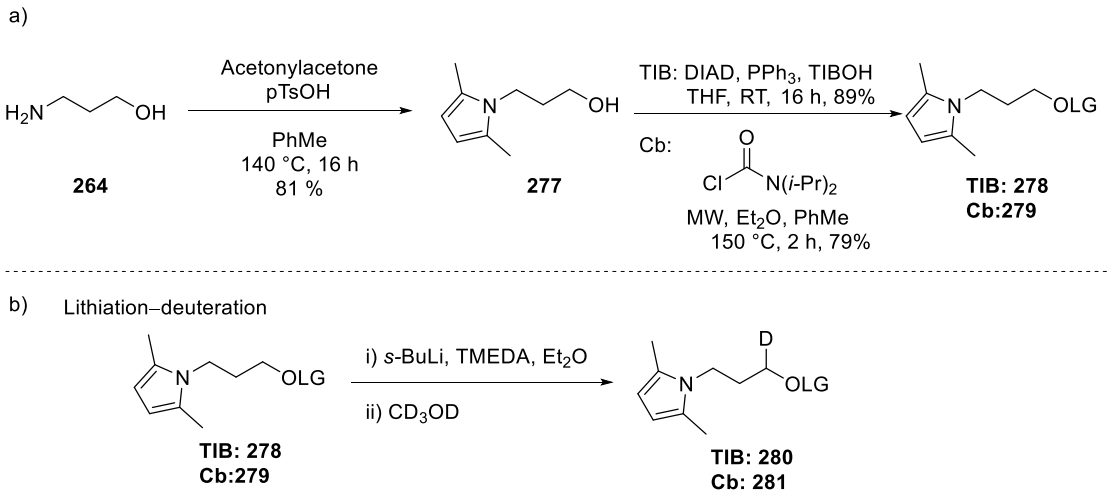
When deprotonation occurs in the presence of (−)-sparteine the pro-(*S*) proton is removed selectively to afford an anion that can be intercepted by electrophiles. Although Beak reported good-to-high yields in all cases, the enantioselectivity was shown to vary substantially depending on the electrophile used.



Scheme 58 Lithiation of a substrate containing an unprotected secondary amide

Development of a Pyrrole Protecting Group

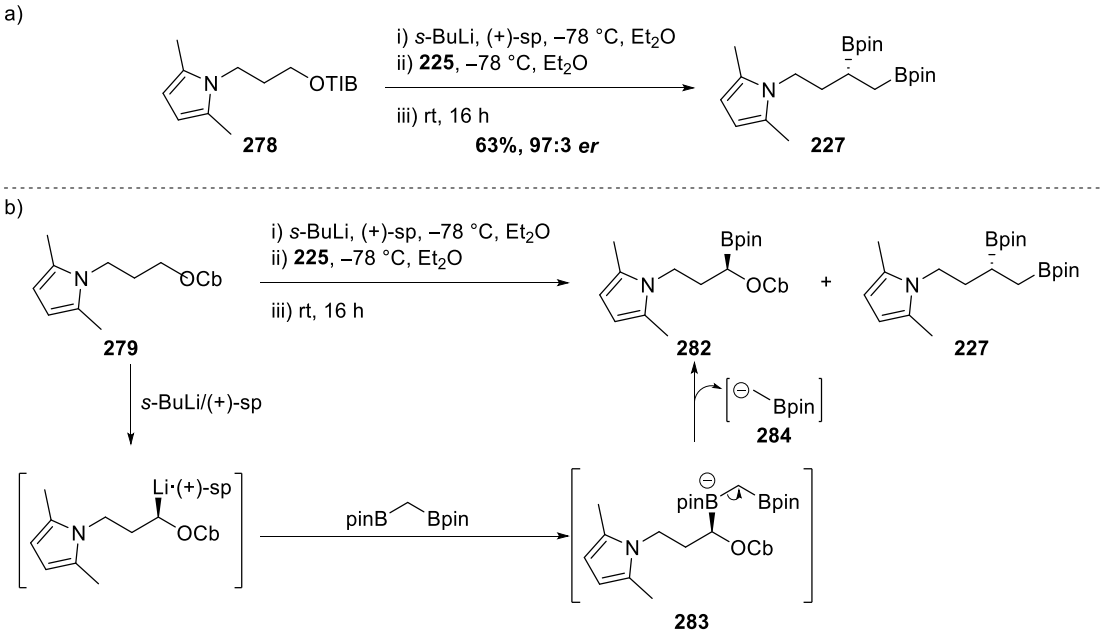
Before investigating the reactivity of carbenoid **272**, it was decided to test the previously problematic lithiation−borylation reaction using a pyrrole with no acidic protons. 2,5-Dimethylpyrroles **278** and **279** were chosen for this role and were synthesised as shown in Scheme 59a from 3-aminopropanol (**264**). Formation of the pyrrole moiety was achieved through a Paal-Knorr reaction with acetonylacetone to generate alcohol **277**, which was transformed into benzoate **278** and carbamate **279** in high yields using procedures previously described for the synthesis of **266** and **267**. The lithiation of pyrroles **278** and **279** were evaluated in a lithiation−deuteration study (Scheme 59b). Pleasingly, full deuterium incorporation was observed for both benzoate **278** and carbamate **279** after a lithiation period of 3 h, as determined by ^{1}H NMR analysis.



Entry	Leaving group	D incorporation / %
1	benzoate	100
2	carbamate	100

Scheme 59 Lithiation–deuteration of compounds **278** and **279**

The diboration of carbenoid precursors **278** and **279** was then attempted (Scheme 60). Gratifyingly, ^{11}B NMR analysis showed that boronate complex formation occurred for both benzoate **278** and carbamate **279**. In the case of carbamate **279**, migration was afforded by heating the reaction mixture overnight at 35 °C; whereas the reaction mixture was stirred overnight at ambient temperature for the benzoate. Crude GCMS analysis suggested the exclusive formation of the desired product (**227**) in the benzoate reaction, which was isolated in 63% yield and with 97:3 *er* (Scheme 60a). However, in the carbamate reaction **227** was contaminated with another species with a mass that corresponded with compound **282**. Formation of **282** could plausibly occur through decomposition of boronate complex **283** to generate stabilised α-boryl anion **284**. Given this result, benzoate **278** was taken forward for further studies.

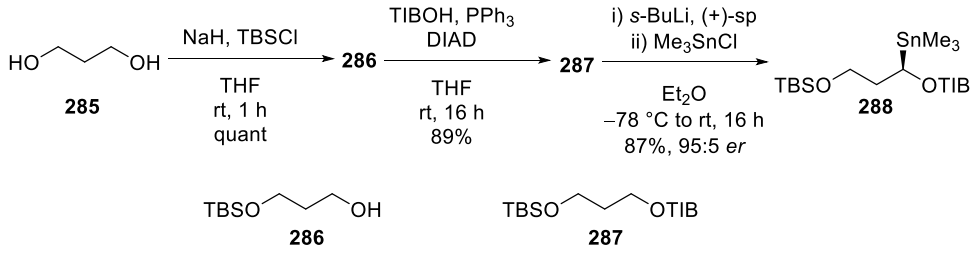


Scheme 60 Lithiation–borylation of benzoate **278** and carbamate **279** with diborylmethane, with proposed degradation pathway for the carbamate

Key Step

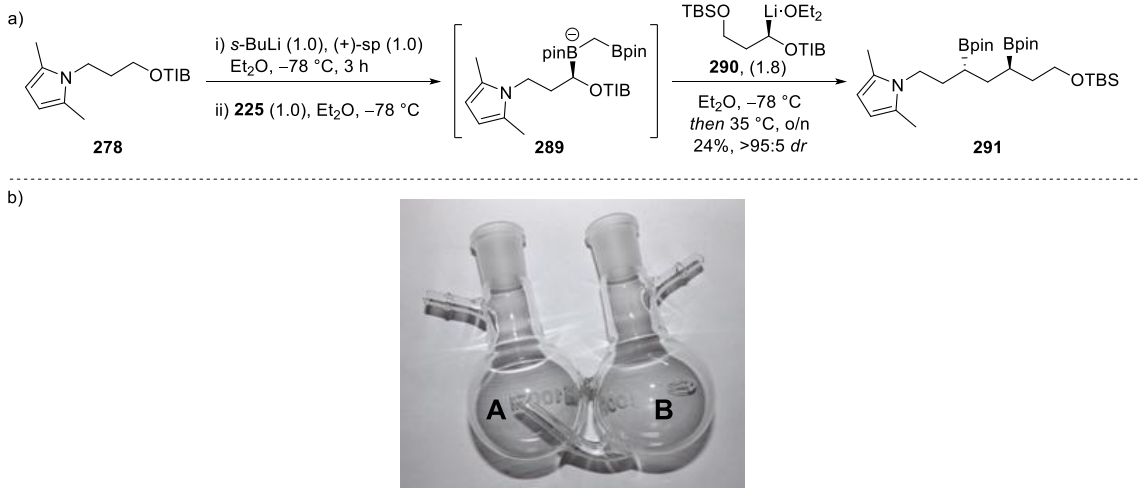
With the benzoate established as the optimum leaving group, the key coupling between pyrrole **278**, diborylmethane (**225**) and α-stannyl benzoate **288** was then investigated. The synthesis of α-stannyl benzoate **288** was achieved in three steps from 1,3-propane diol (**285**). Deprotonation of **285** with one equivalent of sodium hydride and quenching with TBSCl afforded monoprotected alcohol **286** in quantitative yield. Conversion into benzoate **287** was achieved under Mitsunobu conditions in high yield. Finally, stannane **288** was furnished through stereoselective deprotonation of benzoate **287** with *s*-BuLi and

(+)-sparteine followed by trapping of the organolithium with Me_3SnCl with retention of stereochemistry (Scheme 61).



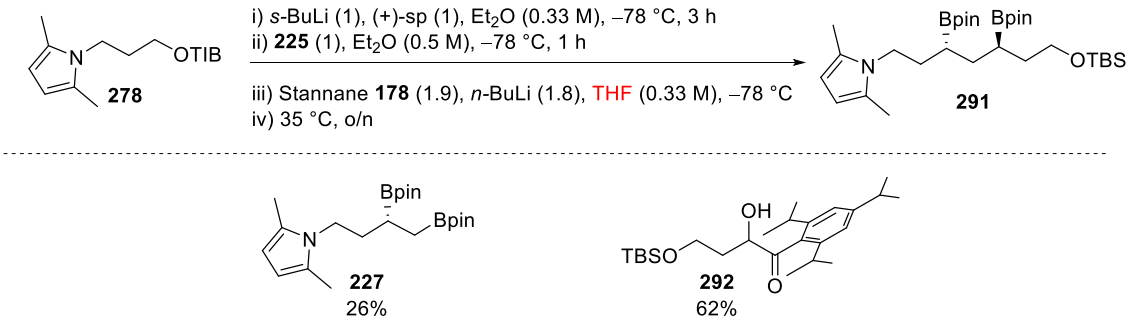
Scheme 61 Synthesis of stannane **288**

Practically, the coupling of fragments **278**, **225** and **288** is challenging because the corresponding carbenoids must be formed separately and then combined at −78 °C to prevent decomposition that is observed above −40 °C. Owing to this constraint it would be difficult to add carbenoid **273** *via* a syringe or cannula, and so our group's own custom glassware was used for this purpose (Scheme 62b). The lithiation of pyrrole **278** required the use of precious (–)-sparteine to obtain the correct diastereomer of atorvastatin derivative **223**; however, to not waste (–)-sparteine anti-diastereomer **291** was selected as the model compound for this coupling. Lithiation of benzoate **278** and formation of boronate complex **289** was achieved in the **A** side of the vessel at –78 °C. Concurrently, in the **B** side, tin−lithium exchange of stannane **288** afforded carbenoid **290**. Following the requisite time, **290** was tipped into the compartment containing the first boronate complex **289** while still at −78 °C. After a further hour at −78 °C, the reaction mixture was heated at 35 °C for 16 h. Gratifyingly, on the first attempt, the product (**291**) was isolated in 24% yield (Scheme 62a).



Scheme 62 Model lithiation–borylation reaction between diborylmethane and carbenoid precursors **278** and **288**

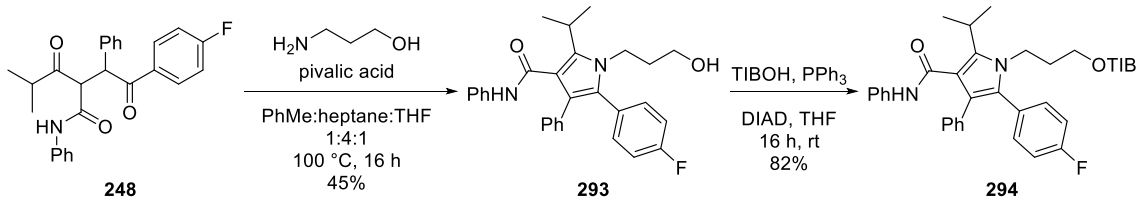
Because the formation of compound **227** proceeds in good yield (64%) the logical place to aim our efforts at optimisation was the formation of the second boronate complex. Upon formation of boronate complex **289**, the (+)-sparteine that was coordinated to the carbenoid derived from benzoate **278** becomes free within the reaction mixture. If formation of the second boronate complex is indeed slow, this adventitious (+)-sparteine may coordinate to carbenoid **290**, reducing its nucleophilicity. By performing the tin−lithium exchange in THF (a better coordinator than Et_2O but similar to (+)-sparteine), the putative coordination of (+)-sparteine to carbenoid **290** may be retarded and thus allow for a greater amount of boronate complex formation (Scheme 63). Unfortunately, under these conditions no product was observed. After purification, 1,2-bis(boronic ester) **227** and rearranged carbenoid **292** were obtained. Formation of 1,2-bis(boronic ester) **227** suggests that formation of the initial ate complex occurred as expected. The presence of rearranged carbenoid **292** suggests that THF is a competent solvent for tin−lithium exchange; however, the carbenoid furnished is not sufficiently nucleophilic to form a boronate complex or the boronate complex formed is reversible in THF. As a result, the carbenoid decomposed, forming α-hydroxy ketone **292**, upon warming to room temperature. Because compound **291** was obtained when using Et_2O as solvent, albeit in low yield, it was decided to move on to optimising the reaction to obtain target **223**.



Scheme 63 Reaction of diborylmethane with carbenoid precusors **278** and **288** using THF as solvent for the tin–lithium exchange

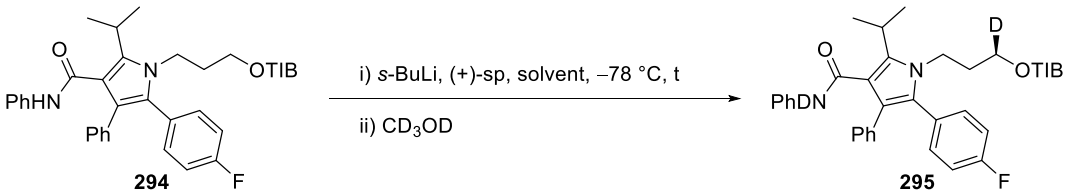
Application of model studies to the real system

Synthesis of benzoate **294** was achieved in two steps from 3-aminopropanol and commercially available diketone **248**. Emulation of the highly specific Paal–Knorr reaction described by Roth,[74,75] yielded advanced pyrrole **293**, which was subjected to a Mitsunobu reaction with 2,4,6-triisopropylbenzoic acid to afford benzoate **294** (Scheme 64).



Scheme 64 Synthesis of benzoate **294**

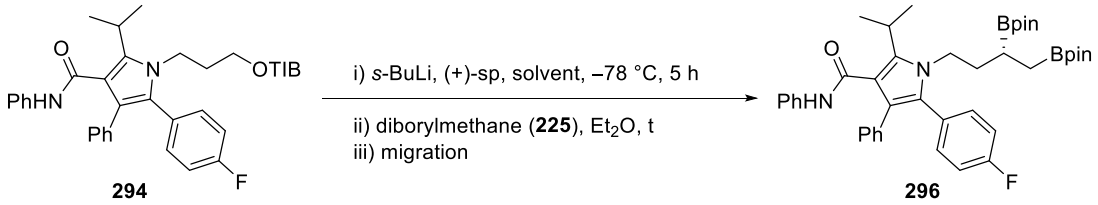
We then evaluated the lithiation of benzoate **294** through lithiation–deuteration studies (Table 1). Beak has shown that asymmetric benzylic lithiation in the presence of unprotected secondary amides is possible when using an excess of *s*-BuLi and sparteine.[81] We sought to utilise this approach to protect the secondary amide of **115** *in situ* as its conjugate base. Benzoate **294** proved to be completely insoluble in ethereal solvents at the usual concentration for the lithiation of primary benzoates (0.33 M); however, this problem was overcome by performing the reaction at 0.1 M. Treatment of **294** with 2.0 equiv of *s*-BuLi and (+)-sparteine for 3 h at −78 °C resulted in 55% deuterium incorporation after quenching with CD_3OD, as determined by ^1H NMR analysis (Table 1, entry 1). Increasing the lithiation time to 5 h had a positive influence and resulted in 60% deuterium incorporation (Table 1, entry 2). It has been shown that the level of lithiation can be improved by utilizing CPME or TBME as solvent;[43,53,82] however, in this case these solvents had no effect, with deuterium incorporation remaining at 60% (Table 1, entries 3 and 4). Increasing the number of equivalents of *s*-BuLi and (+)-sparteine to 2.5 resulted in 74% deuteration (Table 1, entry 5), whereas 85% deuterium incorporation was achieved when using 3.0 equivalents of *s*-BuLi and (+)-sparteine (Table 1, entry 6). Although it stands to reason that higher levels of deuterium incorporation could be achieved by further increasing the equivalents of *s*-BuLi and (+)-sparteine, the excess *s*-BuLi would presumably be able to attack the free boronic ester in the boronate complex derived from the addition of diborylmethane to lithiated **294**. We therefore decided to compromise on potential yield by accepting that the lithiation would not go to completion.



Entry	*s*-BuLi equiv	(+)-sp equiv	t / h	solvent	D incorp. / %
1	2	2	3	Et_2O	55
2	2	2	5	Et_2O	60
3	2	2	5	CPME	60
4	2	2	5	TBME	60
5	2.5	2.5	5	Et_2O	74
6	3	3	5	Et_2O	85

Table 1 Lithiation deuteration studies of benzoate **294**

We next investigated the homologation of diborylmethane **225** with benzoate **294** (Table 2). **294** was treated with 2.0 equiv of *s*-BuLi and (+)-sparteine for a lithiation period of 5 h. A solution of **225** in Et_2O was then added and stirred for a borylation period of 1 h. Following this borylation period, the reaction mixture was warmed to ambient temperature and stirred overnight. The desired product **296** was obtained in 12% yield and 18% of the starting material **294** was recovered; however, the rest of the mass balance could not be accounted for (Table 2, entry 1). Increasing the equivalents of *s*-BuLi, (+)-sparteine and diborylmethane had a negative influence on the reaction, resulting in just 4% yield of **296** (Table 2, entry 2). A slight increase in yield (13%) could be obtained by heating the reaction to reflux overnight (Table 2, entry 3); however, this result is no better than the original conditions described in entry 1. Finally, increasing the borylation period from 1 to 2 h also gave no increase in yield (Table 2, entry 4). We did not expect quantitative yield of 1,2-bis(boronic ester) **296** as the lithiation–deuteration studies in Table 1 showed that the maximum level of lithiation that could be achieved when using 2.5 equiv of *s*-BuLi and (+)-sparteine was 74%; however, the observed yields of **296** were not acceptable. The combination of the poor yields of **296** and the failure to be able to account for the mass balance of the reaction suggested that decomposition of a species on the reaction pathway was occurring. As there was no clear way to improve this reaction, we opted to construct **296** using another methodology that was being developed in the group, that merges asymmetric diboration reactions with lithiation–borylation to generate 1,3-bis(boronic esters), which can be converted to 1,3-diols by oxidation.[83]



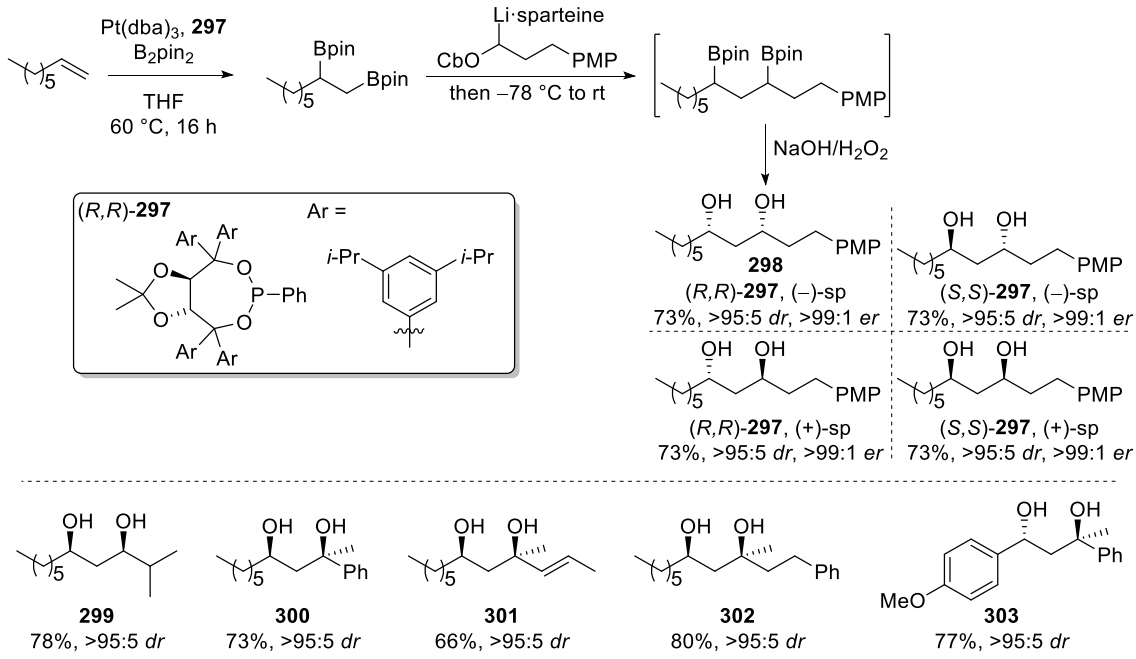
Entry	*s*-BuLi equiv	(+)-sp equiv	**225** equiv	t / h	Migration	Yield / %	RSM / %
1	2	2	1	1	rt, 16 h	12	18
2	2.5	2.5	1.5	1	rt, 16 h	4	6
3	2.5	2.5	1.5	1	35 °C, 16 h	13	8
4	2.5	2.5	1.5	2	35 °C, 16 h	13	13

* RSM = recovered starting material

Table 2 Homologation of benzoate **294** with diborylmethane

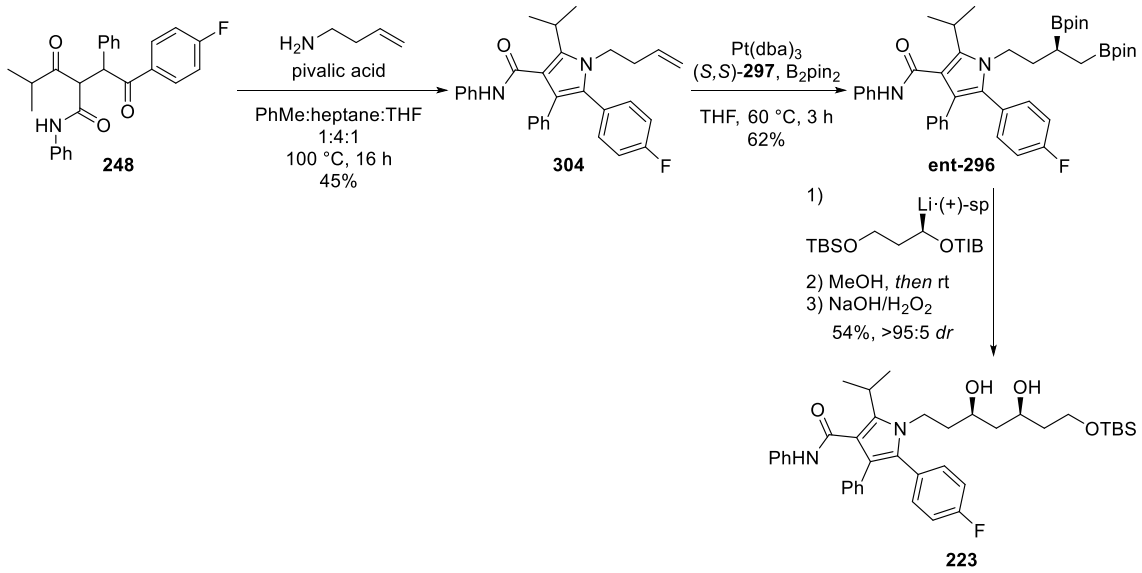
Synthesis of 1,3-diols through a diboration/lithiation–borylation sequence

Aggarwal has shown that the reaction of a 1,2-bis(boronic ester)—derived in enantioenriched form through Morken's asymmetric diboration reaction[75,76] of a terminal alkene—with a (+) or (–)-sparteine coordinated lithiated benzoate or carbamate resulted in a regioselective reaction at the less hindered primary boronic ester to form a single boronate complex at –78 ºC.[83] While the selectivity of this transformation may seem unremarkable—the less hindered primary boronic ester reacts over the more hindered secondary boronic ester—the choice of carbenoid was crucial for the success of the reaction. Employing an unhindered TMEDA ligated- or diamine free-carbenoid resulted in the non-selective formation of a mixture of both boronate complexes resulting from reaction at the primary boronic ester and from reaction at both boronic esters (Scheme 65). Since the enantiomer of 1,2-bis(boronic ester) can be controlled by selection of the appropriate enantiomer of phosphonite ligand **297** and the enantiomer of lithiated carbenoid can be controlled by selection of the appropriate enantiomer of sparteine, it was possible to synthesize all four stereoisomers of diol **298** with good yield and uniformly high diastereo- and enantioselectivities, which demonstrated that the process operated under complete reagent control. Under the standard conditions, primary carbamates and benzoates could be utilized to obtain 1,3-diols, such as **299**, in good yield and with perfect stereoselectivity. Significantly, employing a secondary benzylic or allylic carbamate, or a secondary dialkyl benzoate, permitted the formation of molecules containing adjacent secondary–tertiary 1,3-diols, **300** to **303**. A method for the formation of any diastereomeric permutation of secondary–tertiary 1,3-diols with complete stereocontrol was previously absent from the literature.[84–89]



Scheme 65 Synthesis of 1,3-diols through a diboration/lithiation–borylation sequence

Pyrrole **304** was synthesized through a Paal–Knorr reaction between allyl amine and commercially available 1,4-diketone **248** in 45% yield. Diboration of the terminal alkene of **304** under Morken's conditions generated the required bis(boronic ester) (**ent-296**) in 62% yield; however, despite multiple attempts we were unable to determine the enantiomeric excess of **ent-296** as we could not identify conditions that permitted separation of the enantiomers by chiral HPLC or SFC analysis. Subjecting **ent-296** to the final homologation furnished diol **223** as a single diastereomer after oxidation with basic peroxide and completed our synthesis of an atorvastatin derivative. The high *dr* of **223** shows that the *er* of 1,2-bis(boronic ester) **ent-296** must have been >95:5 as it is known that the homologation of a 1,2-bis(boronic ester) with a lithiated benzoate occurs with complete enantiospecificity of the bis(boronic ester) and operates under complete reagent control. If the *er* of **ent-296** were any lower this would therefore be faithfully reproduced in the *dr* of **223**.



Scheme 66 Synthesis of atorvastatin derivative **223**

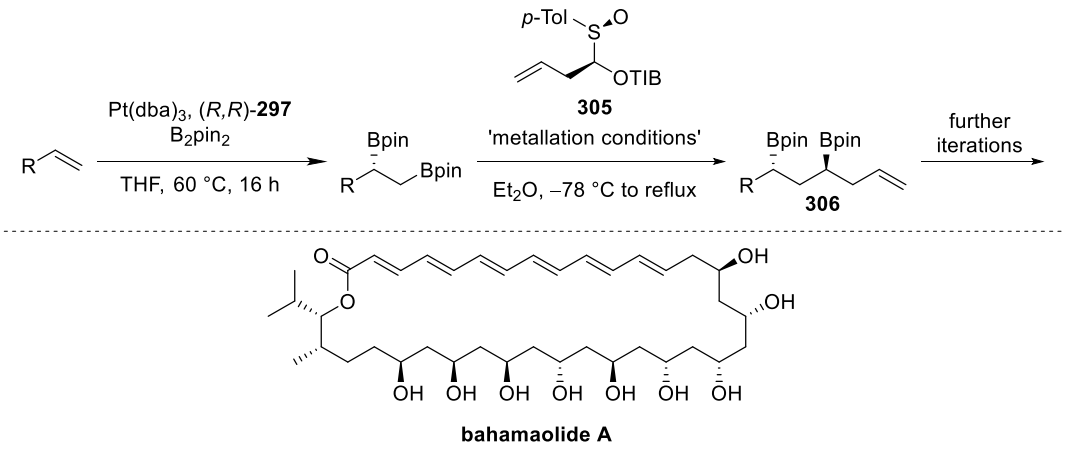
Conclusion

The synthesis of atorvastatin derivative **223** has been achieved in three steps by combining Morken's asymmetric diboration reaction with lithiation–borylation. This procedure operated under complete reagent-control during the lithiation–borylation phase and provided the target molecule with excellent levels of stereoselectivity. It was not possible to synthesise **223** using diborylmethane as linchpin reagent because benzoate **294** was resistant to both lithiation and borylation. While trying to optimize this approach it was shown that 2,5-dimethylpyrrole can be used as a primary amine protecting group that is compatible with lithiation–borylation reactions, thus expanding the scope of this methodology to include substrates containing primary amines.

Chapter 2: Studies Towards the Total Synthesis of Bahamaolide A

Project aim

It has been shown in our group that stereodefined poly(boronic esters) can be accessed in an iterative manner by combining asymmetric diboration reactions and lithiation–borylation reactions, which employ a chiral carbenoid that contains a homoallyl group. Specifically, reaction of an enantioenriched 1,2-bis(boronic ester)—which is derived from a terminal alkene through Morken's asymmetric diboration reaction—with homoallylic sulfoxide **305** generates a 1,3-bis(boronic ester), such as **306**, with a pendent alkene that is primed to undergo a further asymmetric diboration reaction. We aimed to utilise this process to achieve the first total synthesis of the oxopolyene macrolide bahamaolide A (Scheme 67).[2,3]



Scheme 67 Iterative synthesis of 1,3-poly(boronic esters) and bahamaolide A

Introduction to the oxopolyene macrolides

The oxopolyene macrolides are a subset of the polyene macrolide family of compounds, which contains over 200 members.[90] The first polyene macrolide to have its absolute configuration deduced was amphotericin B. In 1970, Schaffner showed that the polyol array of amphotericin B had an all-syn configuration through crystallisation of the *N*-iodoacetyl derivative **307**[91] (Figure 3). By analogy, it was incorrectly assumed that other polyene macrolides also contained all-syn polyols,[92] which led to the publication of a number of methods to generate the syn-polyol motif in an enantioselective manner.

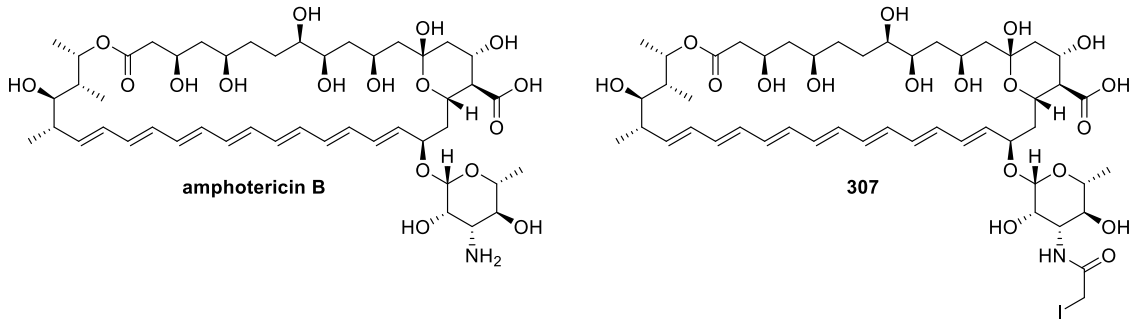
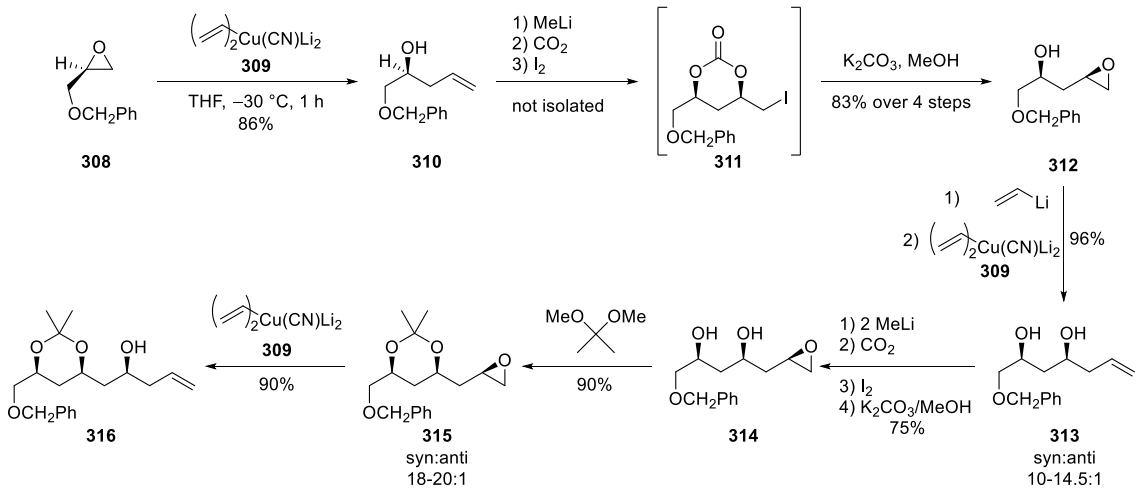


Figure 3 N-iodoacetyl amphotericin B used by Schaffner to determine the absolute configuration of amphotericin B

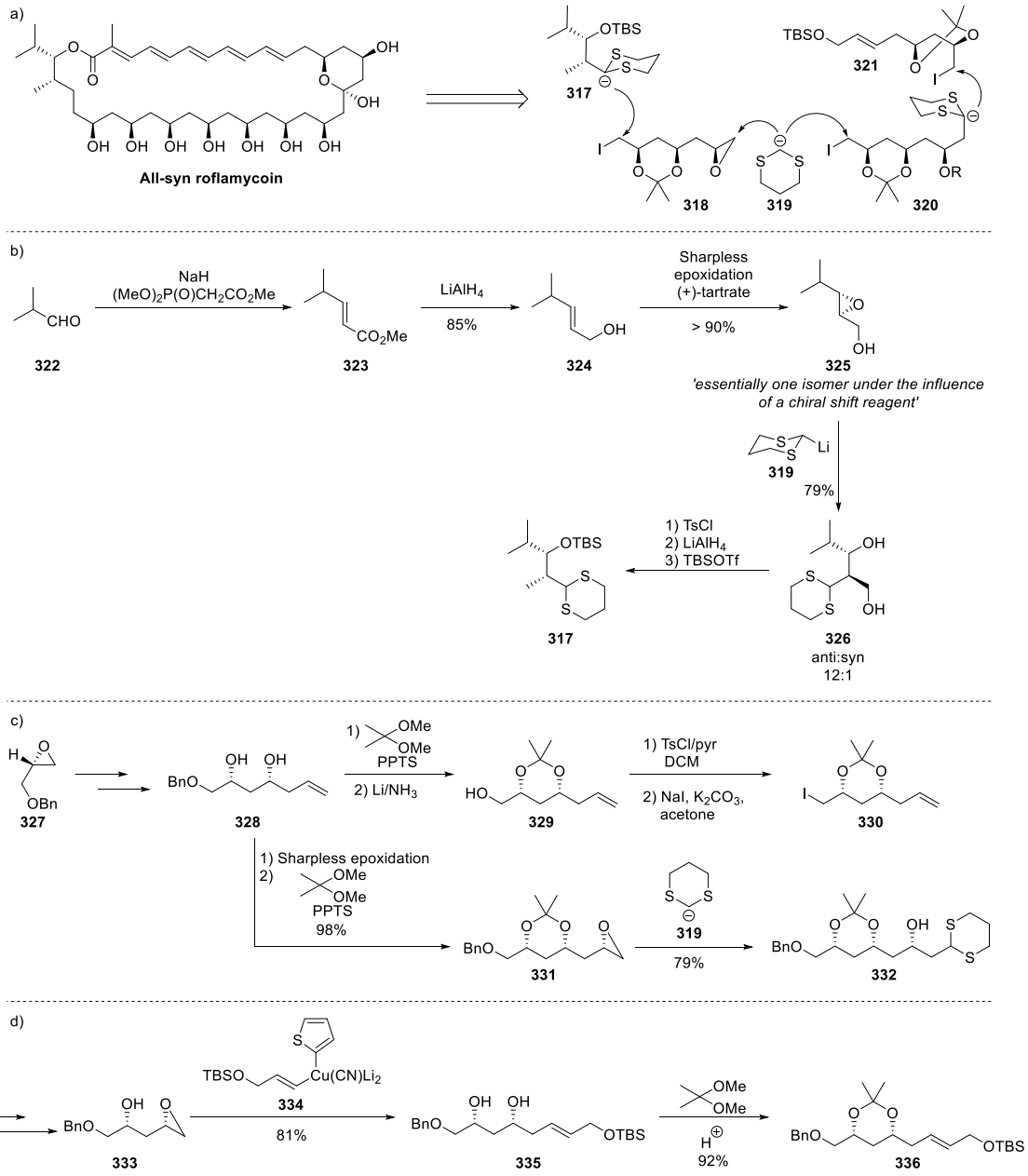
One such method was proposed by Lipshutz, who showed an iterative procedure whereby a chiral epoxide was opened by a high order vinyl cuprate to form a homoallylic alcohol, which was subsequently epoxidised.[93] Addition of high order cuprate **309** to enantioenriched epoxide **308** resulted in the formation of homoallylic alcohol **310** in high yield. Conversion of **310** to epoxide **312** was achieved through a Cardillo epoxidation;[94] specifically, carbonate formation followed by substrate directed attack of the alkene, after activation with iodine, to afford intermediate **311**. Treatment of **311** with base resulted in cleavage of the carbonate and subsequent ring closing yielded epoxide **312**, which is primed for re-entry into the iterative cycle. Homoallylic alcohol **316** was obtained following a further iteration with this methodology (Scheme 68).



Scheme 68 Lipshutz's literative synthesis of enantiopure syn-1,3 polyols

Lipshutz sought to showcase this methodology in the synthesis of all-syn roflamycoin.[95] Retrosynthetic analysis revealed polyol containing fragments **318** and **320**, which were to be coupled together using dithiane **319** as a one-carbon linchpin. Fragments **317** and **321** were also to be installed through alkylation chemistry with the corresponding dithianes (Scheme 69a). Synthesis of dithiane **317** was achieved in seven steps from isobutyraldehyde. HWE olefinatation followed by reduction yielded allylic alcohol **324**,

which was subjected to Sharpless epoxidation conditions to yield epoxide **325** in high yield and as a single enantiomer. Opening of the epoxide with dithiane **319** furnished diol **326**, which was converted to **317** through elimination of the primary alcohol (Scheme 69b). Polyol **328** is a common intermediate in the synthesis of fragments **330** and **332**, and was constructed using the iterative strategy shown in Scheme 68. **330** was achieved in a further four steps from **328** through protection of the 1,3-diol, reductive removal of the benzyl ether, activation of the hydroxyl group and a Finkelstein reaction. **332** was achieved through Sharpless epoxidation of the homoallyl group and subsequent ring opening with dithiane **319** (Scheme 69c). The final fragment was made by opening epoxide **333** with high order cuprate **334** to afford elaborated homoallylic alcohol **335**, which could be used as a functional handle to install the polyene moiety. **336** was then achieved through protection of the 1,3-diol as the acetonide (Scheme 69d). Despite successfully synthesising fragments **317**, **330**, **332** and **336**, Lipshutz did not publish the coupling of these fragments and so the perception that oxopolyene macrolides contained syn-polyols remained.



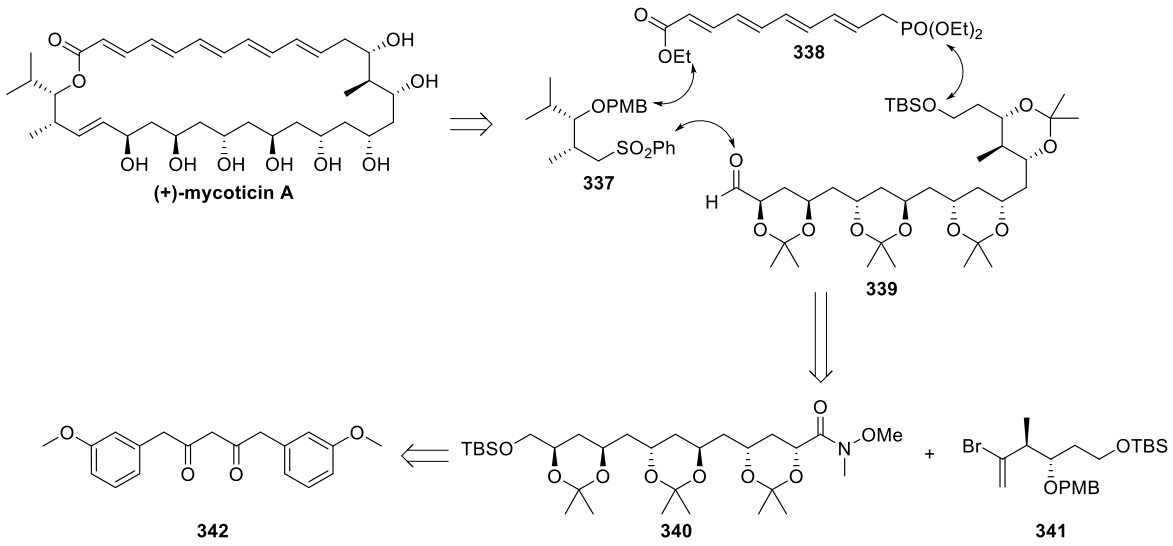
Scheme 69 Lipshutz's synthesis of fragments **317**, **318**, **320** and **321** *en route* to all-syn roflamycoin

The correct configurations of mycoticin, roxaticin and roflamycoin were later deduced by Schreiber[7,8] Maehr[98] and Rychnovsky,[99] respectively.

Schreiber's synthesis of (+)-mycoticin

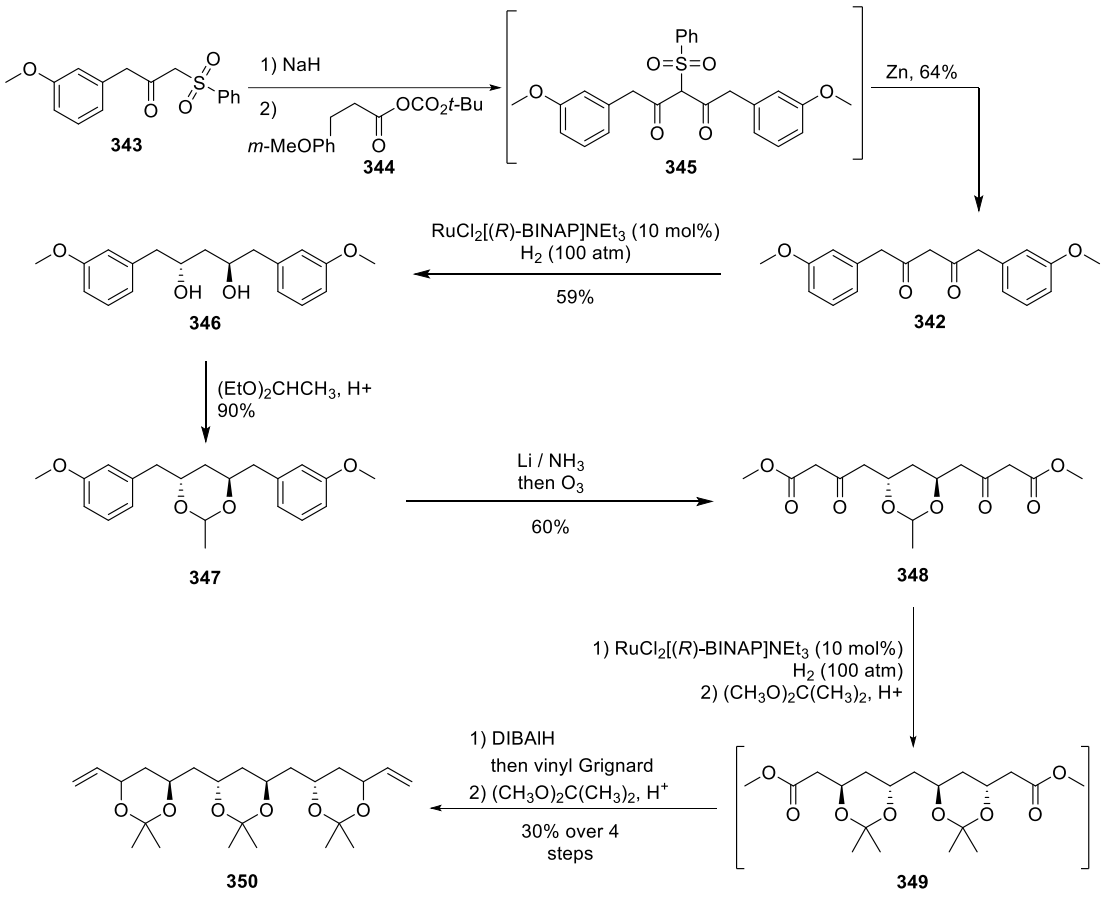
The first oxopolyene macrolide to succumb to total synthesis was mycoticin, which was achieved by Schreiber.[100] Schreiber's retrosynthetic analysis revealed fragment **339** as the key component, which contained the stereodefined hydroxyl array. The unsaturation at C-29 would be installed through a Julia olefination reaction with sulfone **337** and the polyene region would be installed through a HWE reaction with polyene containing fragment **338**. Final macrolactonisation would conclude the synthesis. Key polyol

containing fragment **339** could be obtained from Weinreb amide **340**, which contains a protected C_2-symmetric polyol array, and vinyl bromide **341**. Weinreb amide **340** could be achieved in enantioenriched form through a bi-directional chain extension strategy from diketone **342** (Scheme 70).



Scheme 70 Schreiber's retrosynthetic analysis of mycoticin A

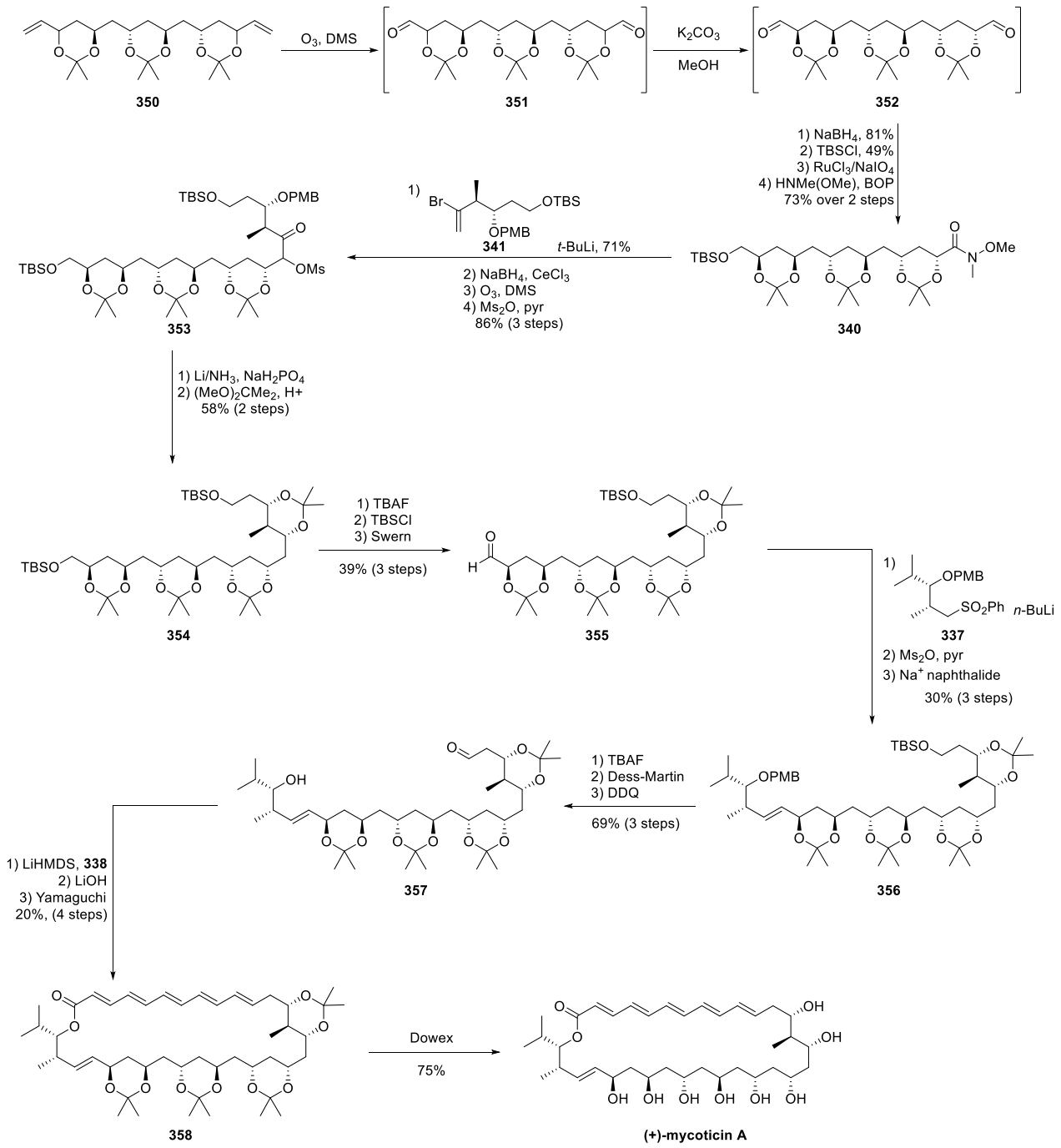
Diketone **342** was achieved from sulfone **343** through acylation with mixed anhydride **344** followed by reductive desulfuration with zinc. Asymmetric ketone reduction using Noyori's method and protection as the methyl ketal afforded protected diol **347** as a single stereoisomer. Conversion of the *meta*-methoxylphenyl groups to β-ketoesters was achieved through a dissolving metal reduction of the aromatic groups and subsequent ozonolysis in 60% yield. Reduction of the β-ketoesters using Noyori's method and acetonide protection afforded diester **349**, which was reduced to the dialdehyde without isolation and subsequently vinylated and protected to yield hexaol **350** in 30% yield over 4 steps (Scheme 71).



Scheme 71 Schreiber's synthesis of compound **350**

Hexaol **350** was converted to Weinreb amide **340** in 6 steps. Ozonolysis of **350** afforded dialdehyde **351**. The two final stereocentres of **240** were set by base catalysed epimerisation of **351** that favoured the C_2 symmetric adduct **352**. Reduction of both aldehydes with $NaBH_4$ preceded a desymmetrising mono-protection of one terminal alcohol, which proceeded in statistical yield. Oxidation of the remaining hydroxyl group using Ley's conditions and amide formation yielded Weinreb amide **340**. Acylation of the vinyl anion derived from fragment **341**, Luche reduction, ozonolysis and mesylation resulted in compound **353** in 86% yield. Simultaneous removal of the mesylate and PMB ether, and reduction of the ketone with >15:1 syn:anti selectivity with lithium in buffered ammonia resulted in a 1,3-diol that was protected as the acetonide to yield **354** in 58% yield over two steps. Deprotection of both silyl ethers, reprotection of the less hindered primary hydroxyl group and oxidation of the remaining alcohol furnished aldehyde **355** in 39% yield over three steps. Installation of fragment **337** was achieved through a Julia olefination reaction, which installed the C-29 unsaturation, to give **356** in 30% yield over three steps. **356** was converted to **357** through a series of oxidation level changes and protecting group manipulations, which was subsequently reacted with phosphonium salt

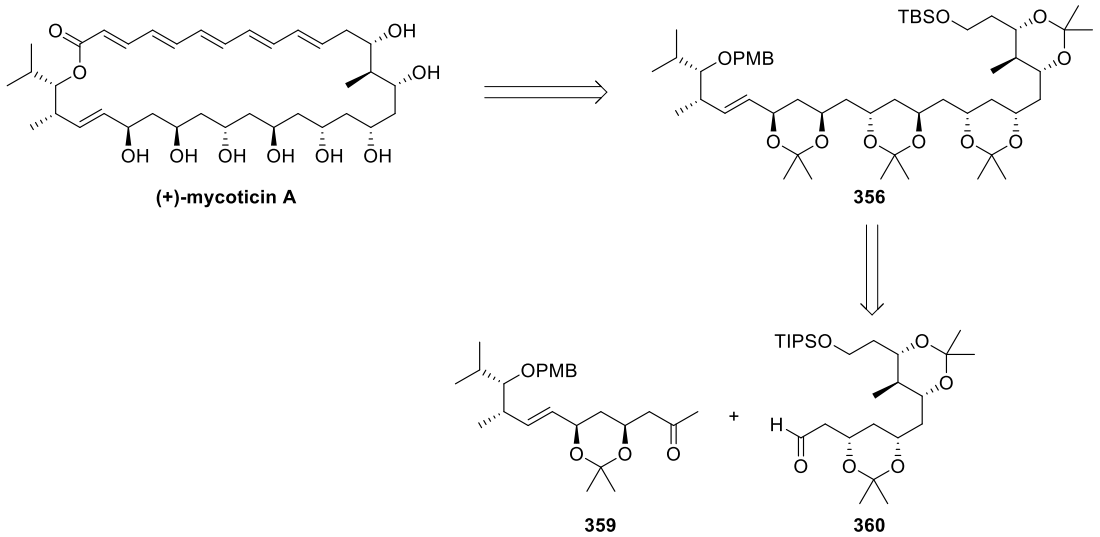
338, saponified and subjected to macrolactonisation conditions described by Yamaguchi to afford acetonide protected mycoticin A, **358**, in 20% yield over four steps. Global deprotection of the acetonides with dowex resin afforded (+)-mycoticin in a total of 35 steps as the longest linear sequence (Scheme 72).



Scheme 72 Schreiber's synthesis of (+)-mycoticin A

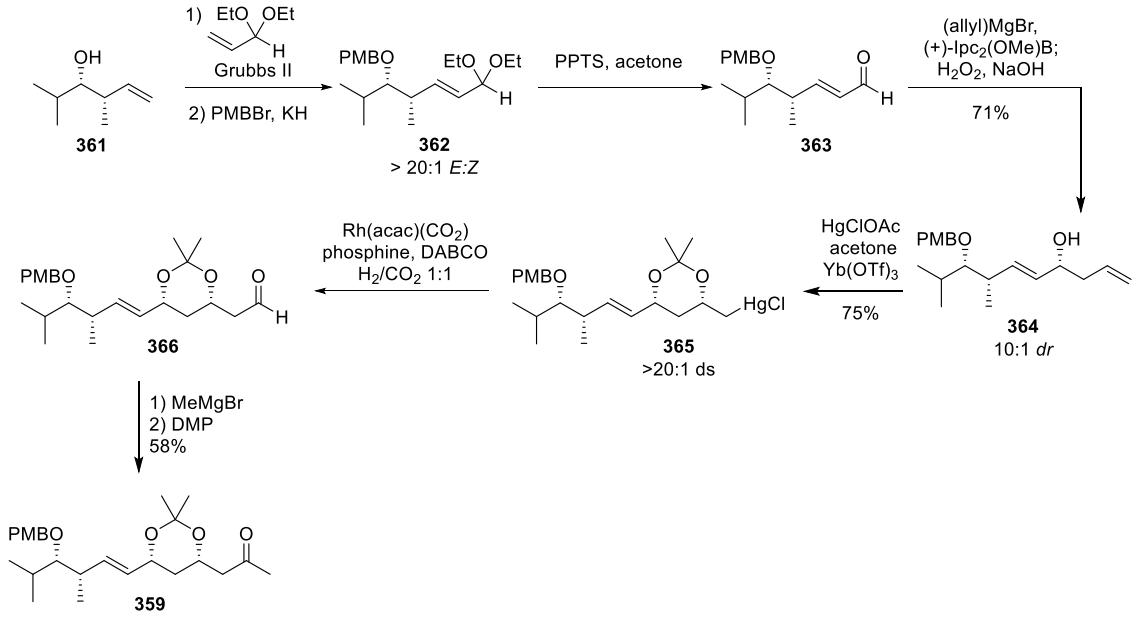
Leighton's formal synthesis of (+)-mycoticin A

Leighton achieved a formal synthesis of (+)-mycoticin A by synthesising the Schreiber intermediate **356** using a diastereoselective aldol reaction to join fragments **359** and **360** (Scheme 73).[101]



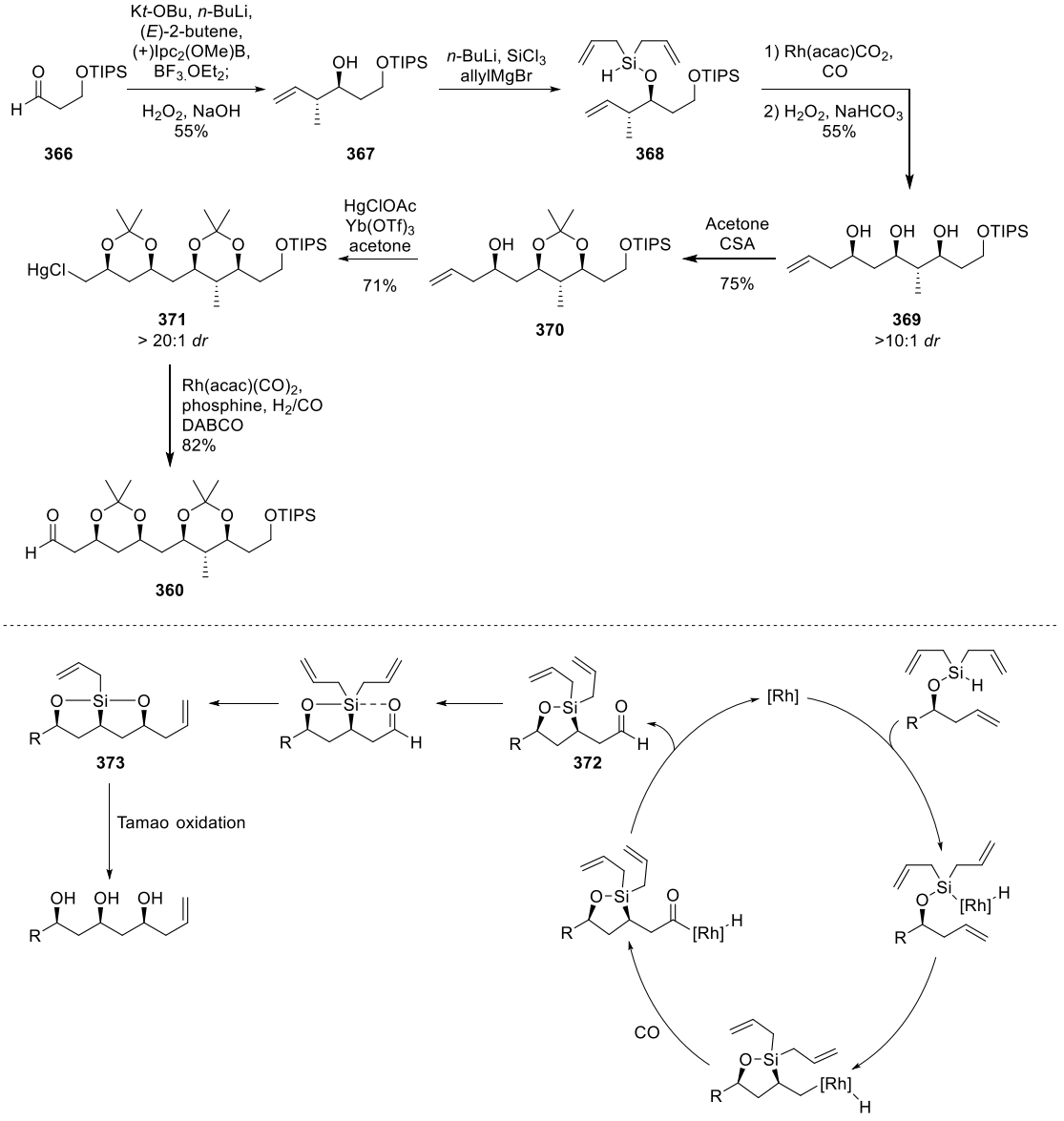
Scheme 73 Leighton's retrosynthetic analysis of the Schrieber intermediate, **356**

Fragment **359** was synthesised from known alcohol **361**[102] in eight steps. Cross metathesis of **361** with diethoxyacrolein followed by protection of the alcohol as the PMB ether gave alkene **362** with > 20:1 *E:Z* selectivity. Hydrolysis of the acetal with PPTS in acetone furnished aldehyde **363**, which was subjected to Brown's asymmetric allylation conditions to yield homoallylic alcohol **364** in 71% yield over four steps and with 10:1 *dr*. Substrate directed Leighton oxymercuration yielded syn-acetonide **365** with no erosion of diastereomeric ratio. Rhodium catalysed formylation of **365** proceeded through oxidative addition of rhodium into the carbon–mercury bond, insertion of CO and reductive elimination to generate aldehyde **366**. Conversion of the aldehyde to the methyl ketone was achieved through addition of a Grignard and subsequent oxidation to yield **359** in 58% yield over three steps (Scheme 74).



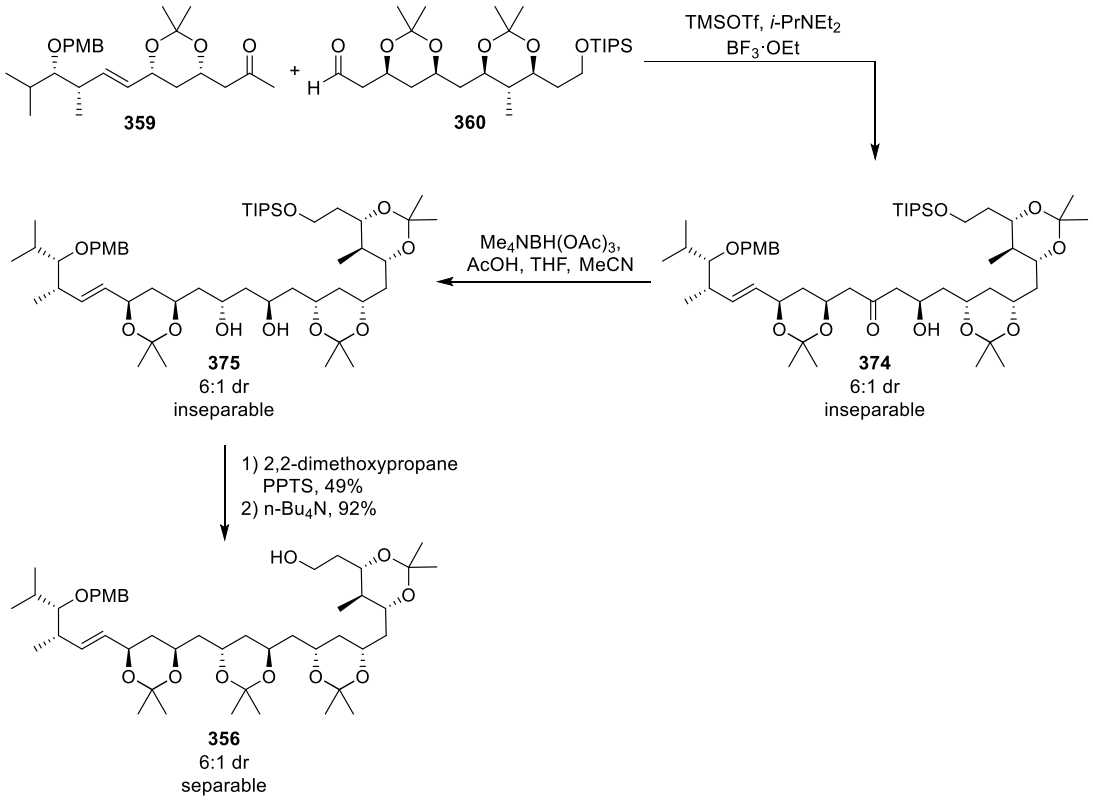
Scheme 74 Synthesis of fragment **359**

Aldehyde **360** was synthesised from known aldehyde **366**[103] in seven steps. Asymmetric crotylation of **366** using Brown's protocol yielded homoallylic alcohol **367**, which was converted to diallylsilylane **368**. Rhodium catalysed silylformylation and subsequent oxidation of the silyl group afforded tetraol **369** in 55% over four steps and with >10:1 *dr*. The silylformylation proceeded through oxidative addition of rhodium into the Si–H bond, insertion to the alkene, formylation and reductive elimination of a hydride to generate **372**, which underwent a spontaneous syn-allylsilylation reaction to generate homoallylic alcohol **373**.[104] Stereospecific Tamao oxidation then yielded the desired tetraol. Installation of an acetonide furnished homoallylic alcohol **370,** which underwent a syn-Leighton oxymercuration reaction and subsequent formylation to yield fragment **360** in 82% yield and > 20:1 *dr* (Scheme 75).



Scheme 75 Synthesis of aldehyde **360**

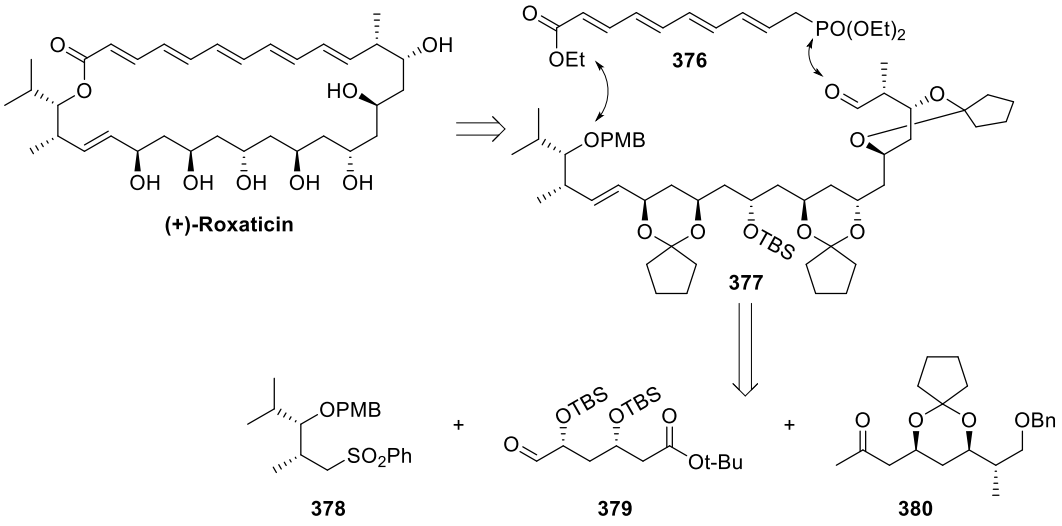
Synthesis of the Schreiber intermediate was completed by coupling fragments **356** and **360** with a Mukaiyama aldol reaction, which is known to furnish the 1,3-anti products when using methyl ketones and β-alkoxy aldehydes.[15,16] In the event, treatment of **359** and **360** with TMSOTf, Hünig's base and $BF_3{\cdot}OEt_2$ yielded aldol product **374** as an inseparable mixture of diastereomers. Anti-selective reduction of the ketone using tetramethylammonium triacetoxyborohydride afforded compound **375**, also as an inseparable mixture of diastereoisomers. Installation of an acetonide and deprotection of the terminal silyl ether completed the synthesis and yielded the Schreiber intermediate **356** in 22 steps and with an overall yield of 1.1% (Scheme 76).



Scheme 76 Completion of the synthesis of the Schreiber intermediate **356**

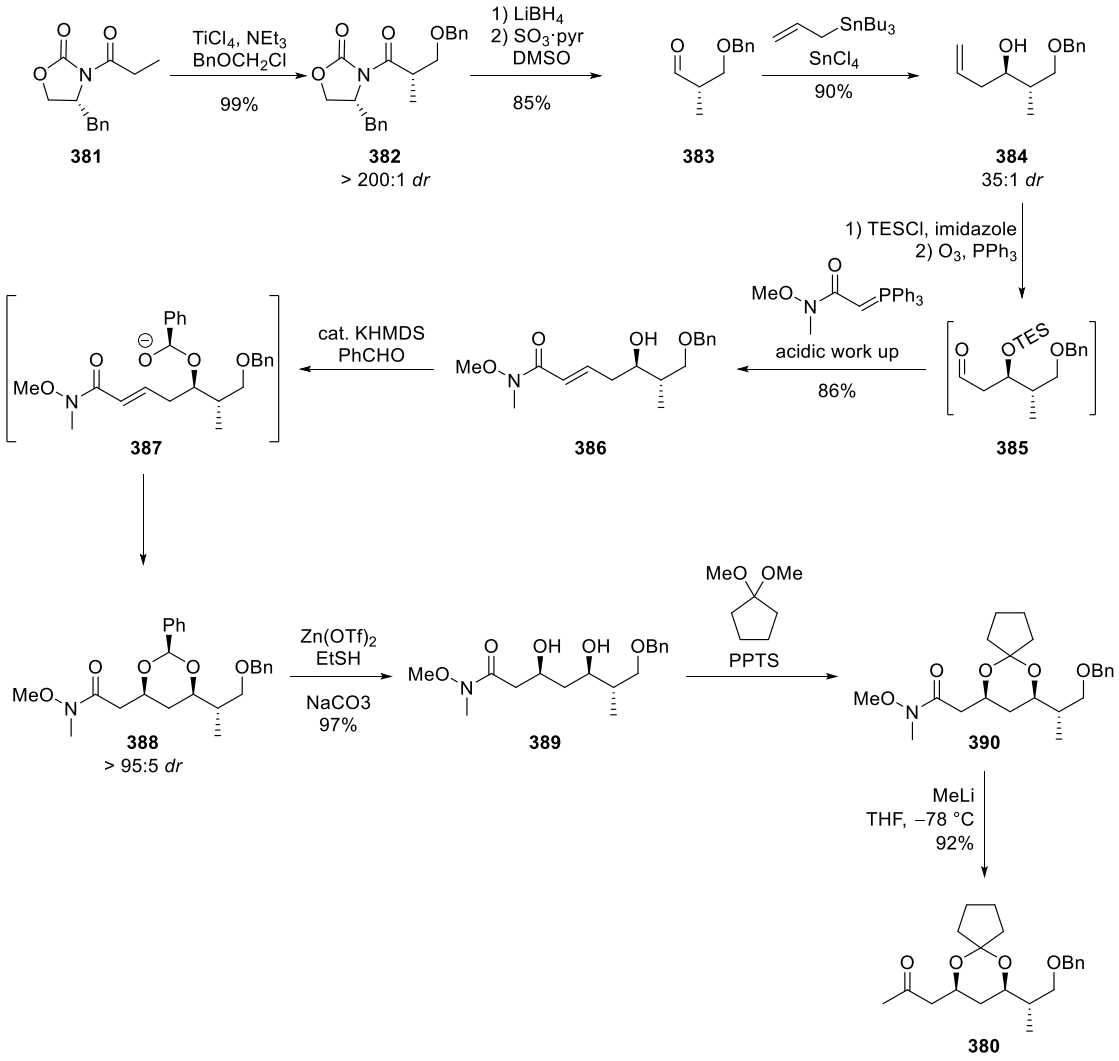
Evans' synthesis of (+)-roxaticin

Evans' retrosynthetic analysis of (+)-roxaticin[107] revealed advanced polyol containing fragment **377**, which underwent HWE reaction and macrolactonisation with polyene containing phosphonate **376** to arrive at the natural product. Further disconnection of **377** led to compounds **378**, **379** and **380**, which were coupled together using a Julia olefination and a diastereoselective 1,3-anti aldol reaction (Scheme 77).



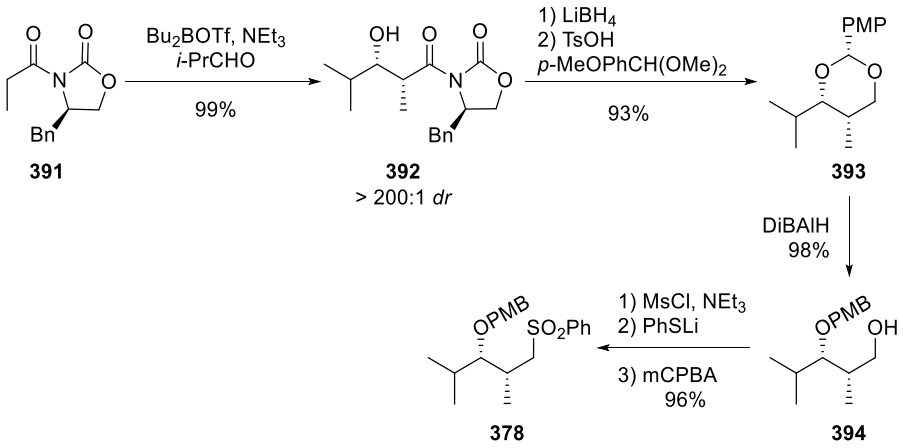
Scheme 77 Evans' retrosynthetic analysis of (+)-roxaticin

Fragment **380** was synthesised from propionyl oxazolidinone **381** in 11 steps. An alkylation reaction between **381** and ((chloromethoxy)methyl)benzene afforded oxazolidinone **383** in quantitative yield and > 200:1 *dr*. Reductive removal of the chiral auxiliary and Parikh-Doering oxidation yielded aldehyde **383**, which was subjected to an allylation reaction using tributylallyl stannane to afford homoallylic alcohol **384** in 35:1 *dr*. Protection of the hydroxyl group, oxidation of the alkene and subsequent Wittig reaction generated homoallylic alcohol **386** in 86% yield. Addition of benzaldehyde resulted in the formation of alkoxy intermediate **387**, which underwent substrate directed conjugate addition to afford protected 1,3-diol **388** with >95:5 *dr*. Installation of a cyclopentyl ketal protecting group and methylation of the Weinreb amide furnished fragment **380** as a single diastereoisomer (Scheme 78). Cyclopentyl ketals were superior to the corresponding acetonides in this case as acetonide deprotection was low yielding.



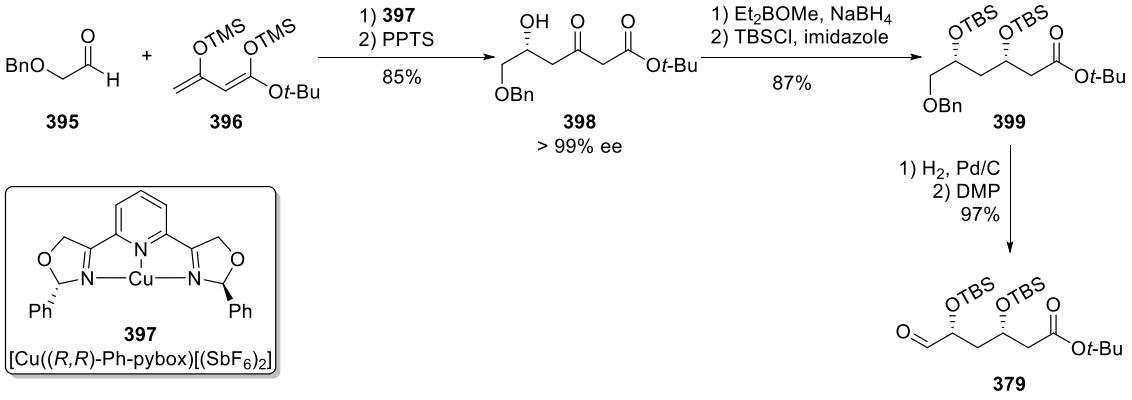
Scheme 78 Synthesis of ketone **380**

The synthesis of sulfone **378** began with an Evans auxiliary directed aldol reaction with isobutraldehyde to furnish alcohol **392** with > 200:1 *dr*. **378** was generated as a single diastereomer through a further sequence of reductive removal of the oxazolidinone group, selective PMB protection of the secondary alcohol, sulfuration and oxidation to the sulfone (Scheme 79).



Scheme 79 Synthesis of sulfone **378**

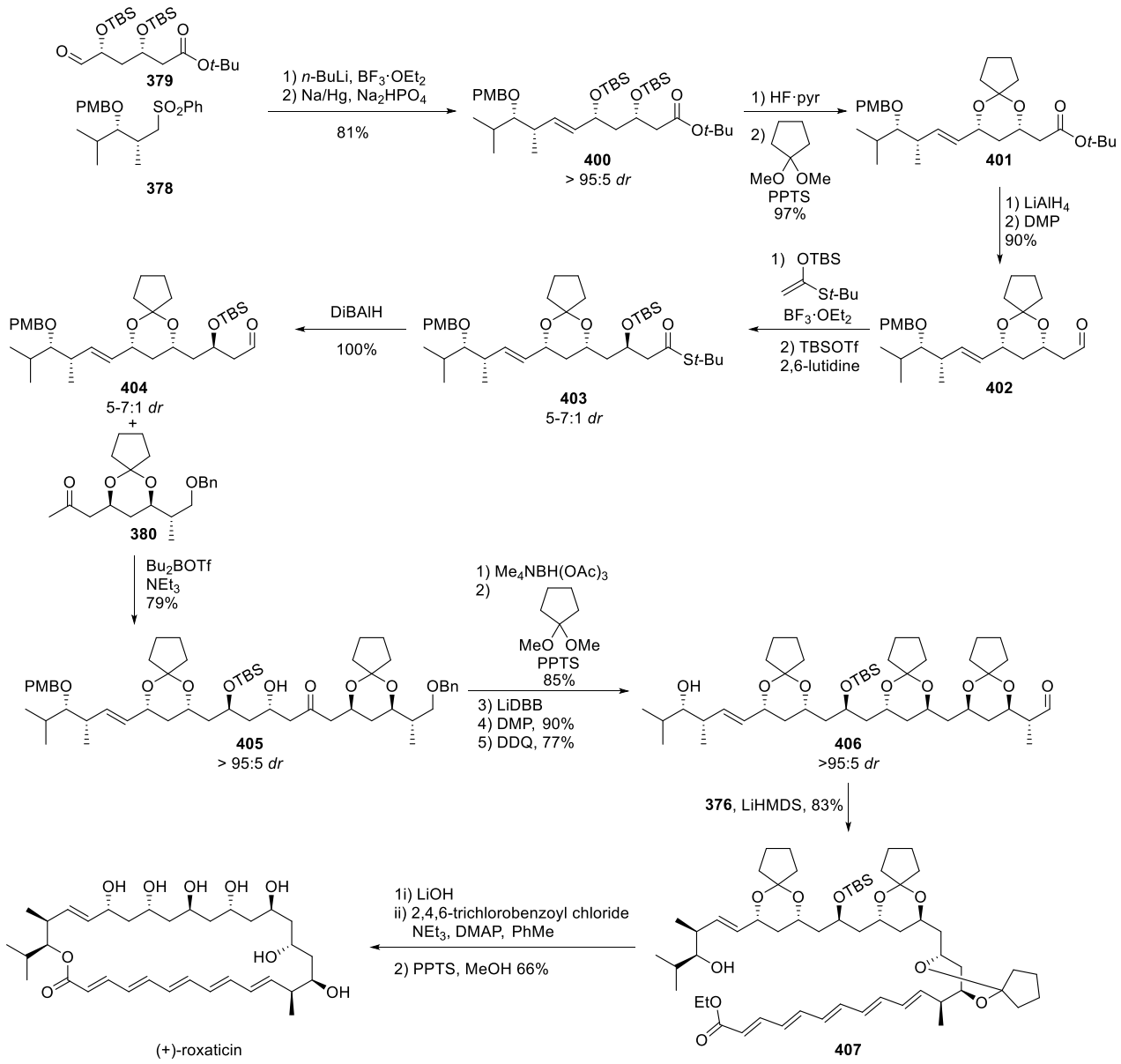
The synthesis of fragment **379** was achieved in six steps from aldehyde **395**. An Aldol reaction between **395** and Chan's diene analogue **396** occurred under the chiral influence of the copper-pybox complex **397** to afford β-ketoester **398** in > 99% *ee* after demasking of the silyl ethers with PPTS. Selective syn reduction of **398** occurred upon treatment with Et_2BOMe and $NaBH_4$ to afford the syn-diol, which was bis-protected with TSBCl to give **399**. Reductive removal of the benzyl ether and oxidation of the alcohol with Dess-Martin periodinane afforded aldehyde **379** in almost quantitative yield (Scheme 80).



Scheme 80 Synthesis of aldehyde **397**

The coupling of fragments **378** and **379** was achieved using a Julia olefination to afford alkene **400** with >95:5 *dr*. Exchange of alcohol protecting groups from silyl ethers to a

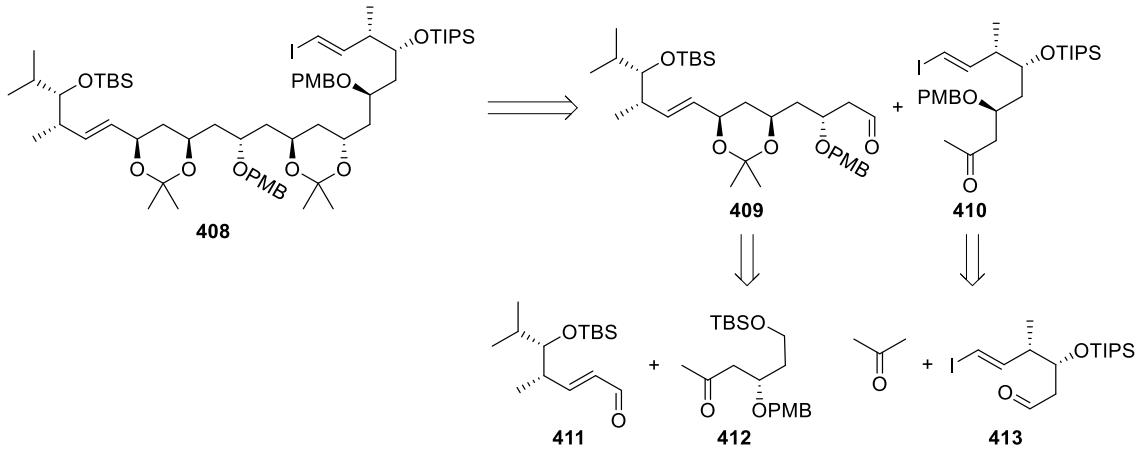
cyclopentyl ketal was required for high selectivity in the 1,3-anti aldol reaction between aldehyde **402** and silyl enol ether **400** as β-siloxyaldehydes give poor diastereofacial control.[106] In the event, the 1,3-anti aldol reaction proceeded to yield ketal **403** as an inseparable mixture of diastereomers after protection as the silyl ether. Reduction of **403** with DiBAlH yielded aldehyde **404**, which was subjected to a 1,5-anti boron aldol reaction with **380** to generate aldol adduct **405**. Kinetic resolution of the diastereoisomers of **405** occurred during the reaction to yield the desired adduct as a single diastereomer. Anti-selective reduction of the ketone, installation of the cyclopentyl ketal, reductive removal of the benzyl ether, oxidation to the aldehyde and oxidative removal of the PMB group furnished aldehyde **406**. HWE reaction with polyene containing phosphonate **376** afforded open chain compound **407**, which was saponified, subjected to Yamaguchi macrolactonisation conditions and globally deprotected to afford (+)-roxaticin with 35 steps in the longest linear sequence and with 55 total steps and an overall yield of 0.18%. To prevent decomposition during the macrolactonisation reaction, the mixed anhydride had to be isolated prior to the addition of DMAP and NEt_3. Utilizing cyclopenylketals resulted in superior yields upon deprotection than the corresponding acetonides, which resulted in < 10% of (+)-roxaticin being isolated (Scheme 81).



Scheme 81 Completion of (+)-roxaticin

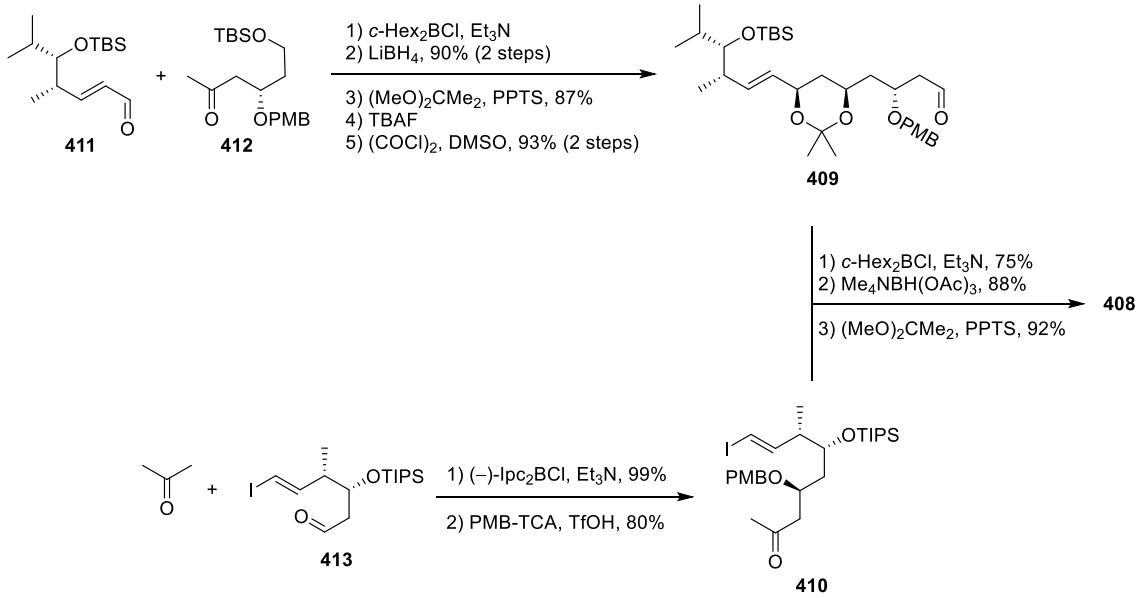
Paterson's synthesis of the polyol region of (+)-roxaticin

Paterson reported the convergent synthesis of fragment **408**, which represents the polyol region of (+)-roxaticin.[108] Retrosynthetic analysis of **408** revealed aldehyde **409** and ketone **410**, which were merged using a diastereoselective 1,5-anti boron aldol reaction.[109,110] **409** and **410** were also made using diastereoslective aldol reactions; specifically, a 1,5-anti boron aldol reaction between aldehyde **411** and ketone **412** was used to generate **409**, whereas a 1,3-syn aldol reaction between acetone and aldehyde **413** was used to access **410** (Scheme 82).



Scheme 82 Paterson's retrosynthetic analysis of the polyol region of (+)-roxaticin (**408**)

The 1,5-anti boron aldol reaction between **411** and **412** and subsequent diastereoselective reduction of the carbonyl proceeded in high yield and diastereospecificity. Acetonide protection, selective cleavage of the primary silyl ether and Swern oxidation yielded aldehyde **409**. 1,3-syn aldol reaction between acetone and aldehyde **413** generated **410** after PMB protection of the secondary alcohol. The key 1,5-anti boron aldol reaction between aldehyde **409** and **410** and subsequent hydroxyl directed anti reduction of the carbonyl using $Me_4NBH(OAc)_3$ generated the desired 1,3-polyol, which was acetonide protected to afford the target compound **408** in 35% overall yield (Scheme 83).

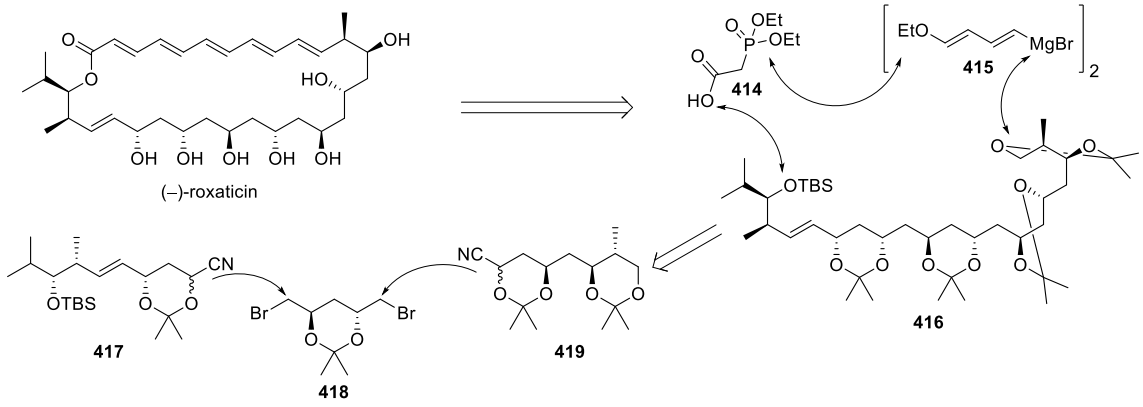


Scheme 83 Paterson's synthesis of compound **408**

Rychnovsky's synthesis of (–)-roxaticin

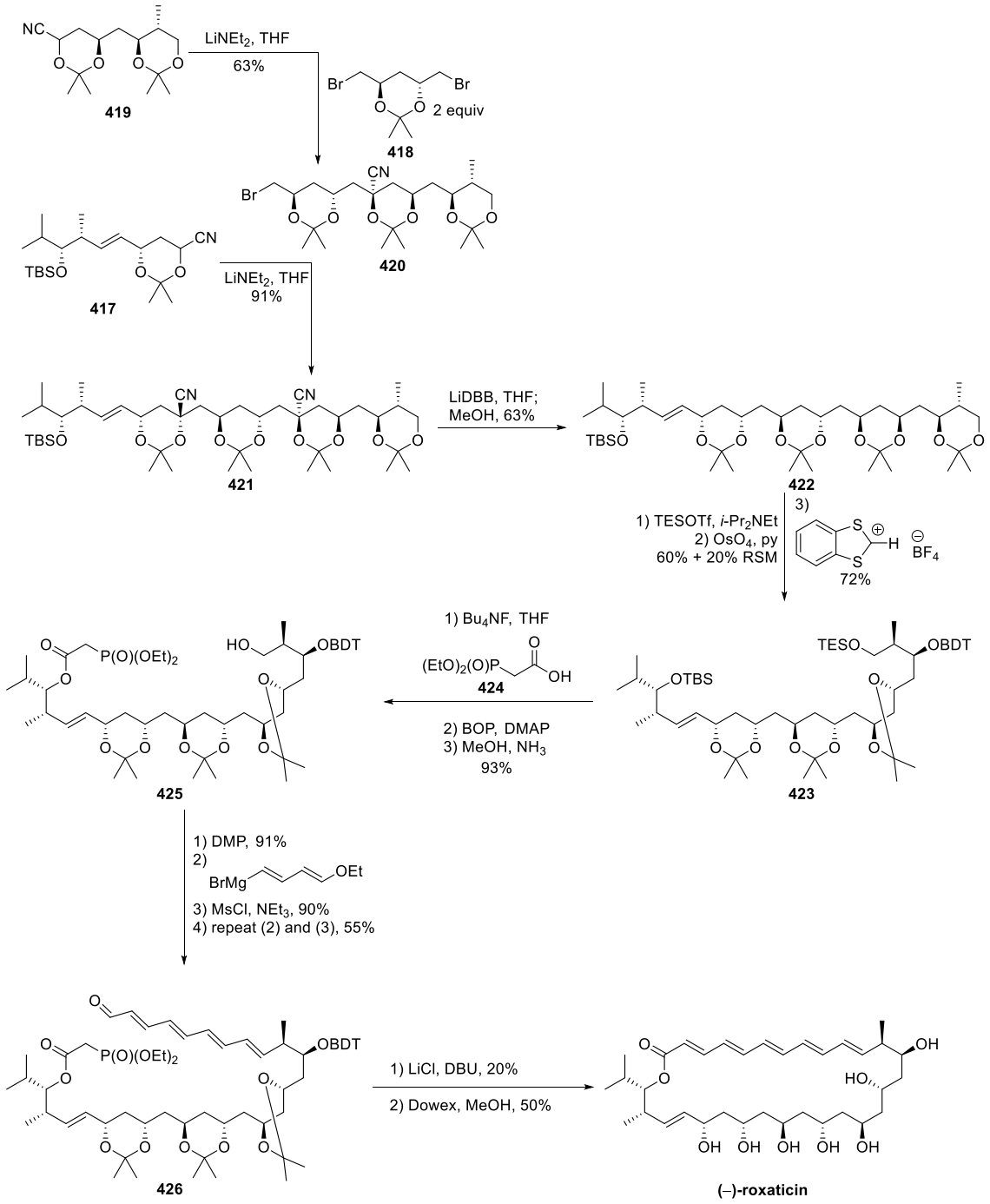
Rychnovsky achieved the total synthesis of the unnatural enantiomer (–)-roxaticin,[111] which was chosen as a tool to study the mode of action of oxopolyene macrolides.

Rychnovsky suggested a convergent strategy to synthesise the polyol motif through the alkylation of cyanohydrin acetonide moieties **417** and **419** with C_2 symmetric dibromoacetonide **418**. The polyene was installed through a series of alkylation reactions using vinyl Grignard fragments, such as **415**, and the macrocycle was formed through a ring closing HWE reaction (Scheme 84).



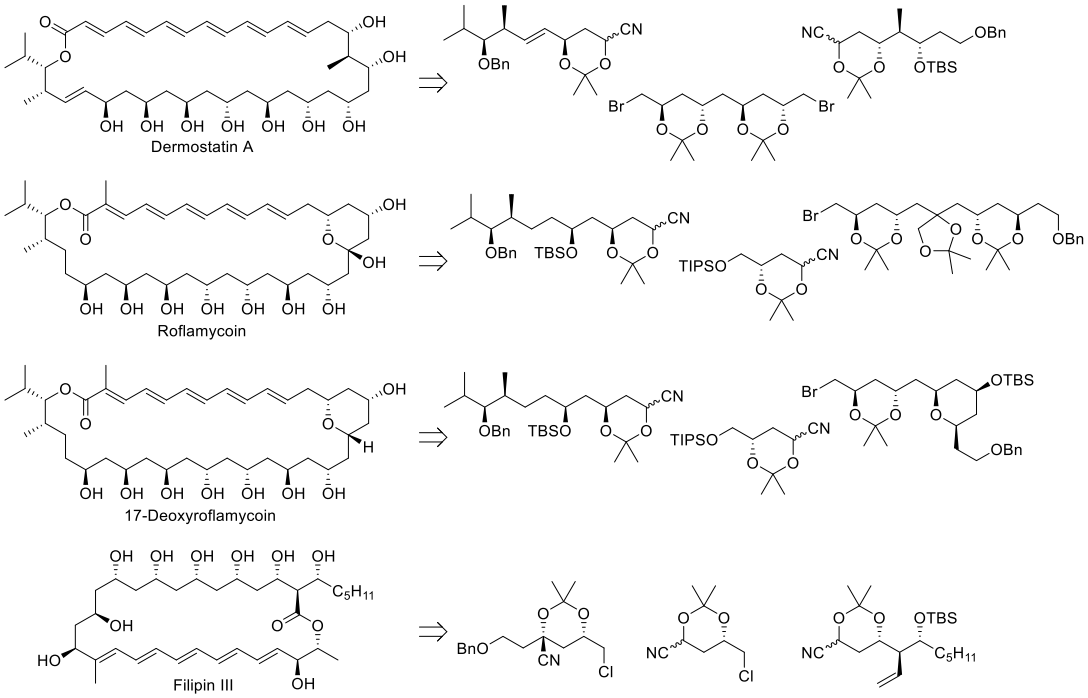
Scheme 84 Rychnovsky's retrosynthetic analysis of (–)-roxaticin

Desymmetrisation of dibromoacetonide **418** with the anion from cyanohydrin acetonide **419** afforded tris(acetonide) compound **420**. This reaction occurred with high selectivity to generate the syn-acetonide,[112] as the nitrile was put in the axial position due to its low A-value following deprotonation. To avoid over-homologation of bis(functionalised) linchpin **418**, a 2.0 equiv excess was used. A second alkylation utilising cyanohydrin **417** generated intermediate **421** in 91% yield, which underwent reductive decyanation with LiDBB to afford polyol containing fragment **422** in 63% yield. Oxidative opening of the terminal acetonide, TES protection of the primary alcohol and protection of the secondary alcohol as the 1,3-benzodithiolan-2-yl ether (BDT) furnished polyol intermediate **423**. The BDT ether was the optimal protecting group as it was not possible to cleave other groups, such as PMB or an enol ether, without destruction of the polyene. Esterification of **423** was achieved through removal of the silyl ethers and treatment with **424**, BOP and DMAP. The primary alcohol was oxidised to the aldehyde and the polyene installed using a modification of Wollenburg's protocol, which afforded conjugated aldehyde **426** after two cycles of Grignard addition. The synthesis was completed with an overall yield of $5x10^{-4}$% following a ring closing HWE reaction using Roush–Masamune conditions and global deprotection of the acid labile protecting groups with Dowex resin (Scheme 85).



Scheme 85 Completion of (–)-roxaticin

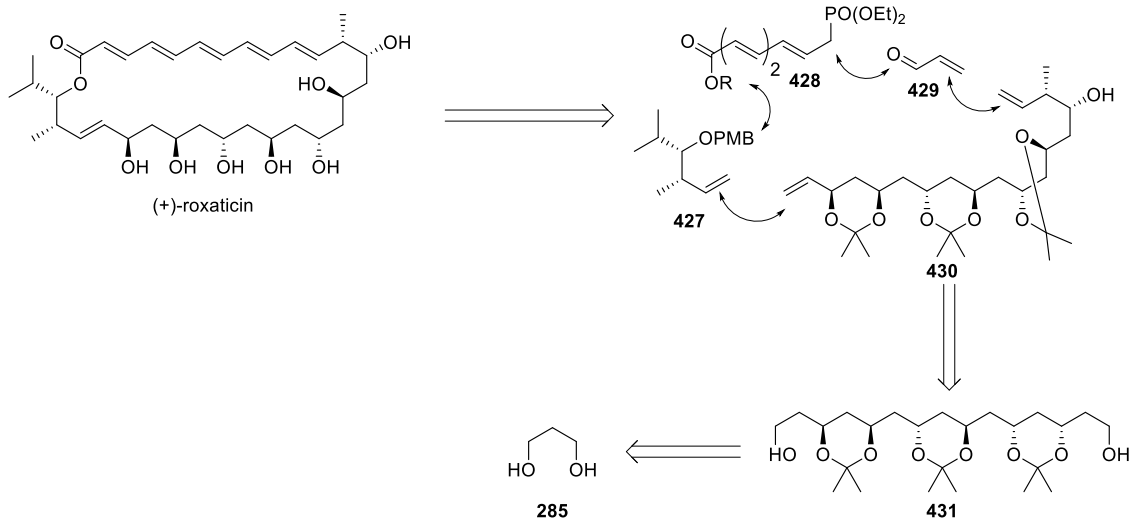
Rychnovsky was able to expand this methodology to the synthesis of dermostatin A, roflamycoin, 17-deoxyroflamycoin and filipin III by altering the acetonide protected cyanohydrin building blocks or the C_2 symmetric linchpin component (Scheme 86).



Scheme 86 Rychnovsky's retrosynthetic analysis of dermostatin A, roflamycoin, 17-deoxyroflamycoin and filipin III

Krische's synthesis of (+)-roxaticin

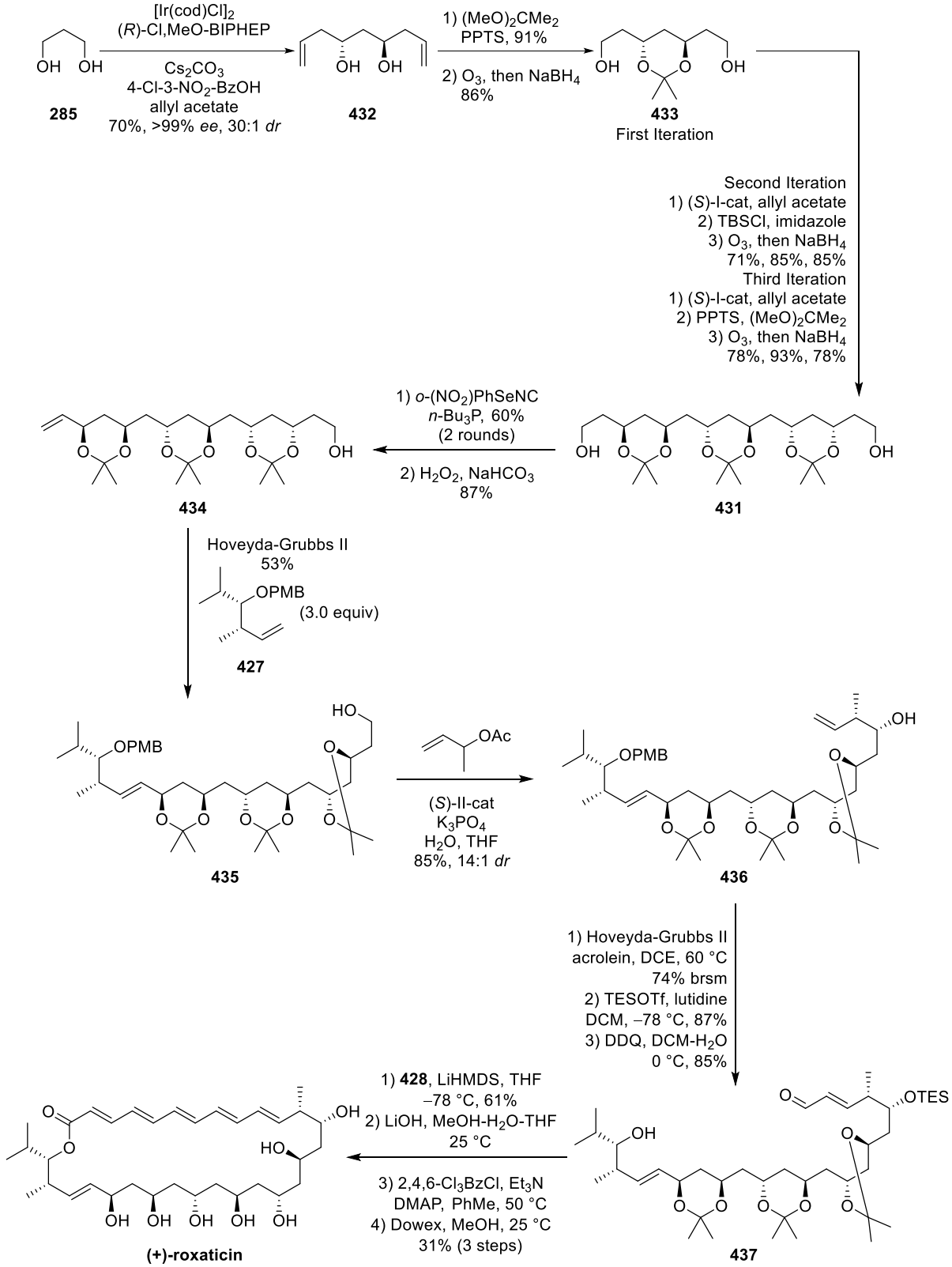
Krische reported the synthesis of (+)-roxaticin, which uses a C–C bond forming transfer hydrogenation reaction as the key step[113] and represents the current state of the art of oxopolyene macrolide syntheses. Notably, the synthesis of the polyol region proceeded with excellent levels of enantio- and diastereoselectivity without the use of chiral auxiliaries. Retrosynthetic disconnections revealed polyol **430** as the key fragment, which was accessed from C_2 symmetric polyol **431**, which in turn was made from 1,3-propanediol (**285**) through a series of iterative, bi-directional allylation reactions directly from the alcohol oxidation level. Installation of the western hemisphere of the molecule and the unsaturation at C-28 was achieved through a cross metathesis reaction with alkene **427**, while the polyene region was incorporated through cross metathesis with acrolein (**429**) followed by a HWE reaction with phosphonate **428** (Scheme 87).



Scheme 87 Krische's retrosynthetic analysis of (+)-roxaticin

The synthesis started with double allylation of 1,3-propanediol (**285**), which proceeded using *ortho*-cyclometallated iridium *C,O*-benzoate, which was generated *in situ* from $[Ir(cod)Cl]_2$, (*R*)-Cl-3-NO_2BzOH and allyl acetate, to generate diol **432** with > 99% *ee* and 30:1 *dr*. The mechanism of this reaction involves initial oxidation of the reactant alcohol to an aldehyde followed by stereoselective allylation of said aldehyde. Remarkably, the *ortho*-cyclometallated iridium *C,O*-benzoate catalyses both the oxidation and allylation phases of the reaction, and does so with near perfect enantio- and diastereoinduction. Protection of diol **432** as an acetonide and ozonolysis with a reductive workup of the resulting aldehyde yielded tetraol **433** in 86%. The iterative cycle of double allylation, protection, oxidation and reduction was then repeated a further two times to yield C_2 symmetric octaol **431** with exquisite levels of enatio- and diastereoselectivity. Desymmetrisation of **431** using a Greico primary alcohol dehydration reaction furnished intermediate **434**, which was primed to undergo cross metathesis with alkene **427** to yield **435** in 53% yield with complete (*E*)-selectivity. Asymmetric crotylation of **435** directly from the alcohol oxidation level gave advanced fragment **436** in high yield and 14:1 *dr*, which underwent subsequent cross metathesis with acrolein, silyl ether protection and PMB deprotection to yield aldehyde **437**. Protection of the C-14 hydroxyl group was vital to permit macrolactonisation; however, cross-metathesis with acrolein did not occur when the alcohol was protected as the silyl ether, presumably due to steric demand. This limitation was easily overcome by performing the cross-metathesis reaction prior to the installation of the silyl ether. The synthesis was completed with a HWE reaction with

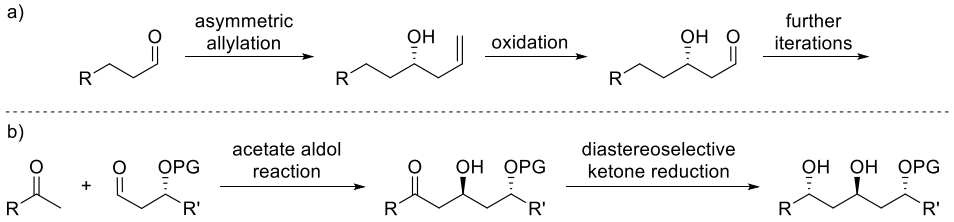
polyene fragment **428**, saponification of the ester, Yamaguchi macrolactonisation and global deprotection to give (+)-roxaticin with an overall yield of 0.74% (Scheme 88).



Scheme 88 Krische's synthesis of (+)-roxaticin

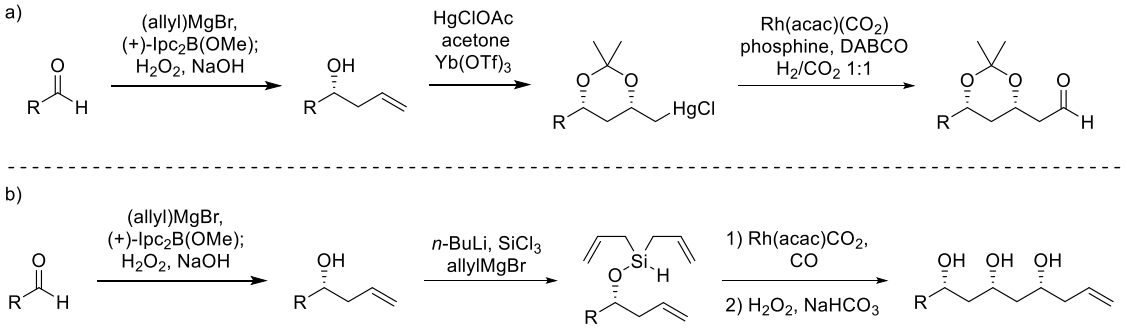
Critical appraisal of the presented literature methods to make oxopolyene macrolides

Commonly, the strategies employed in the synthesis of the 1,3-polyol motif are variations of two approaches; specifically, an asymmetric allylation–oxidation approach (Scheme 89a) or an acetate aldol–diastereoselective ketone reduction strategy (Scheme 89b). The first strategy consists of asymmetric allylation of an aldehyde to give an enantioenriched homoallylic alcohol, which is subsequently oxidised at the alkene to generate a new aldehyde that is ready to engage in a further allylation reaction. The second strategy involves performing a diastereoselective aldol reaction using a methyl ketone enolate to afford a β-hydroxy ketone, which is subsequently reduced to afford a 1,3-*syn* or 1,3-*anti* diol by using either a boron based Lewis acid and sodium borohydride or $NMe_4BH(OMe)_2$, respectively.



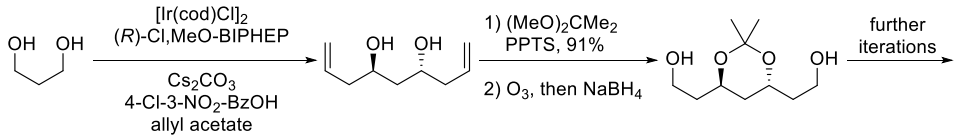
Scheme 89 Common approaches in the synthesis of 1,3-polyols

Leighton presented two variations of the asymmetric allylation–oxidation approach in his formal synthesis of (+)-mycoticin. In the first variation, the oxidation phase was conducted using a substrate directed oxymercuration reaction followed by a rhodium catalysed formylation of the resulting Hg–C bond, which generated a diastereomerically pure *syn* 3,5-dihydroxy aldehyde in two steps from the homoallylic alcohol. (Scheme 90a). This process represented a rapid method to generate β-formyl *syn* 1,3-polyols from homoallylic alcohols in high *dr*, although the use of mercury limits the attractiveness of this methodology. In the second variation, a substrate directed tandem silylformylation–allylation sequence of a homoallylic alcohol, which afforded direct access to a homoallylic *syn* 1,3,5-triol after oxidation of the silyl group (Scheme 90b). The main disadvantage of both strategies was that they operated under substrate control and thus only *syn* 1,3-polyols could be accessed. Moreover, in the allylation phase Leighton utilised Brown's asymmetric allylboration reaction, which is known to be sensitive to stereocentres already present within the molecule and generates isopinocampheol as a by-product, which lowers atom economy and can be difficult to separate from the desired product.



Scheme 90 Leighton's allylation–oxidation sequence

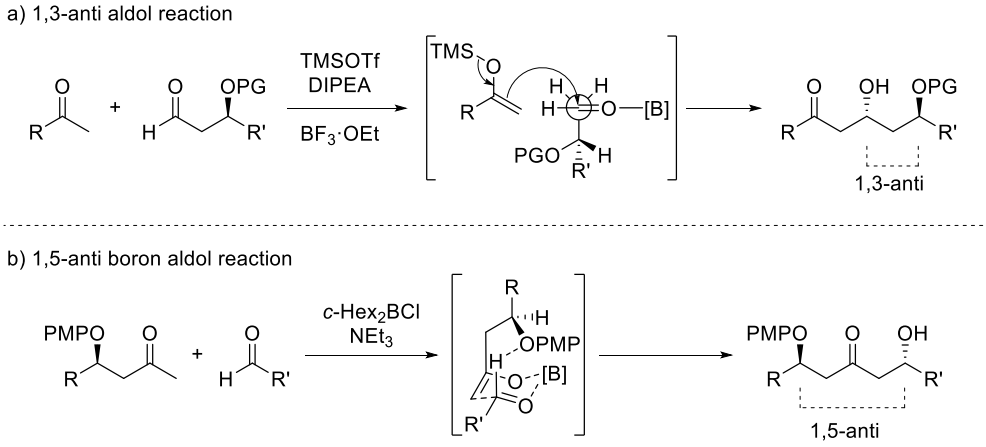
A more attractive process would operate entirely under reagent control so that either enantiomer/diastereomer of the product could be obtained from the same starting material simply by selecting the appropriate enantiomer of chiral reagent. Krische reported the synthesis of (+)-roxaticin using an iridium catalysed allylation reaction which fulfilled this criteria and represents the current state of the art of oxopolyene macrolide synthesis (Scheme 91). The power of Krische's methodology was that either enantiomer of the homoallylic alcohol product could be accessed directly from the corresponding primary alcohol without having to oxidise to the aldehyde prior to functionalisation, thus saving a non-skeletal bond forming manipulation. This was possible because the iridium catalyst was bifunctional; specifically, the catalyst facilitated the in situ oxidation of the alcohol to an aldehyde and also catalysed the asymmetric allylation reaction. Nevertheless, oxidation of the alkene moiety of the homoallylic product was still required to obtain a new primary alcohol for re-entry into the iterative cycle. Using this iterative procedure, Krische was able to synthesise C2 symmetric polyol **431** in a bidirectional manner in just three iterative cycles without the use of premetallated nucleophiles with very high enantio- and diastereocontrol and went on to complete the synthesis of (+)-roxaticin in significantly fewer steps than previously described.



Scheme 91 Krische's allylation–oxidation sequence

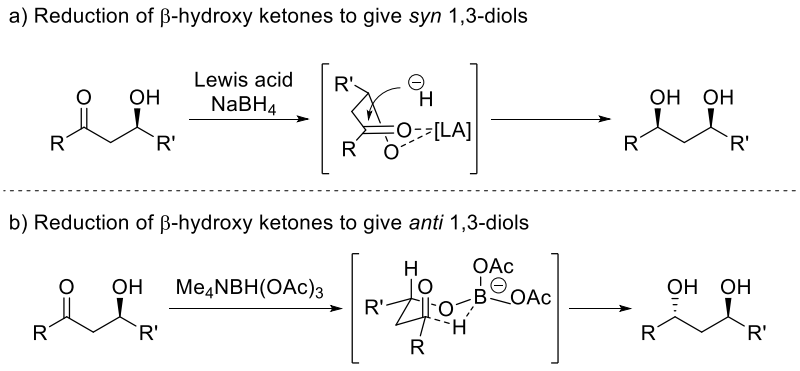
Using aldol chemistry to construct the 1,3-polyol motif is challenging because Evans' oxazolidinone auxiliary does not facilitate the aldol reaction between aldehydes and methyl enolates with high levels of diastereocontrol, which is postulated to be due to loss of diastereotopic face selectivity of the enolate. Nevertheless, a series of substrate

controlled diasteroselective aldol reactions have been developed that can achieve this transformation, for example the 1,3-anti and 1,5-anti boron aldol reactions. In the 1,3-anti aldol reaction a methyl silyl enol ether reacts with a chiral β-hydroxy aldehyde to give 1,3-anti products (Scheme 92). Evans proposed that the reaction proceeded through an open transition state under Felkin–Anh control, where the carbonyl and hydroxyl C–O bonds in the electrophile point in opposite directions in the transition state to limit dipole repulsion. In the 1,5-anti boron aldol reaction a chiral β-hydroxy ketone reacts with an aldehyde using a boron based Lewis acid to give 1,5-anti products (Scheme 92b). In this case, the reaction proceeded through a closed 6-membered transition state, where the β-hydroxyl group of the enolate interacted with the aldehyde to afford the 1,5-anti products.



Scheme 92 Substrate controlled diastereoselective aldol reactions

The reduction of β-hydroxy ketones can be used to afford either 1,3-syn or 1,3-anti diols depending on the conditions employed (Scheme 93). 1,3-Syn diols can be accessed through addition of a Lewis acid and a reducing agent. In this case the Lewis acid chelates the ketone and hydroxyl group to form a 6-membered transition state that the hydride attacks selectively to afford the 1,3-diol (Scheme 93a). 1,3-anti diols can be afforded through reduction with $Me_4NBH(OAc)_3$, whereby delivery of the hydride occurred from within the 6-membered transition state (Scheme 93b).



Scheme 93 diastereoselective reduction of β-hydroxy ketones

Paterson utilised three convergent diastereoselective aldol reactions and subsequent diastereoselective ketone reductions in his synthesis of the polyol region of (+)-roxaticin; specifically, two 1,5-anti boron aldol reactions and a 1,3-syn aldol reaction (Scheme 82). This strategy was very efficient both in terms of step count and overall yield and because the key steps proceeded under substrate control, very high *dr* values were obtained without the use of chiral auxiliaries.

The strategies used by Schreiber and Rychnovsky differed from the others dramatically. Schreiber reported the efficient bidirectional synthesis of compound **350** using Noyori's asymmetric ketone reduction as the stereodetermining reaction (Scheme 71). A key feature of this strategy was the genius use of the PMP group as a masked β-keto ester, which permitted the selective reduction of each pair of carbonyl groups in sequence, thus ensuring the product would be C_2 symmetric. Nevertheless, the synthetic sequence became less efficient after the synthesis of **350** had been achieved, with a significant number of steps being dedicated to protecting group and redox level manipulations that did not form skeletal bonds.

Rychnovsky presented a convergent strategy where the polyol motif of (–)-roxaticin was constructed through the alkylation of cyanohydrin acetonide moieties **417** and **419** with C_2 symmetric dibromoacetonide **418** (Scheme 84). This methodology generated the desired products in high *dr*, but more significantly it could be adapted to generate other members of the oxopolyene macrolide family, which was demonstrated by Rychnovsky in the syntheses of dermostatin A, roflamycoin, 17-deoxyroflamycoin and filipin III (Scheme 86). A disadvantage of this approach was that the syntheses of **417** and **419** were both long (16 and 12 steps, respectively) and that after the polyol moiety had been

constructed a further 13 steps were required to complete the synthesis, which contributed to an overall yield of only 0.0005%.

Studies Towards the Total Synthesis of Bahamaolide A

Bahamaolide A

Bahamaolide A was isolated alongside bahamaolide B from a *Streptomyces* species, cultured from a sediment sample from North Cat Cay in the Bahamas.[2] Bahamaolides A and B differ only in the geometry of the C-13 double bond (Figure 4). Both bahamaolides A and B are 36-membered macrocyclic lactones, which contain a conjugated hexaene and 11 stereocentres, 9 of which form a contiguous 1,3-polyol. Bahamaolide A is an inhibitor of *Candida albicans* isocitrate lyase with an IC_{50} value of 10.8 μM;[3] however, bahamaolide B was completely inactive in the tested biological assays. Currently, neither bahamaolide A nor B have succumbed to total synthesis.

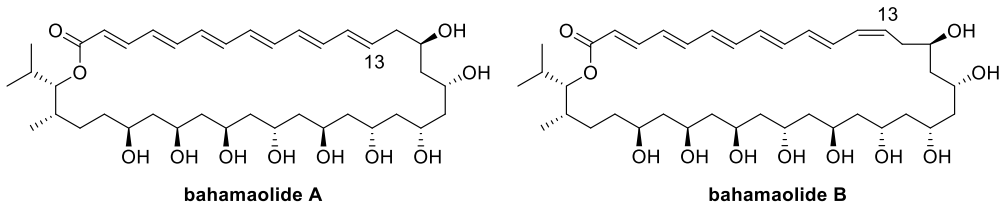
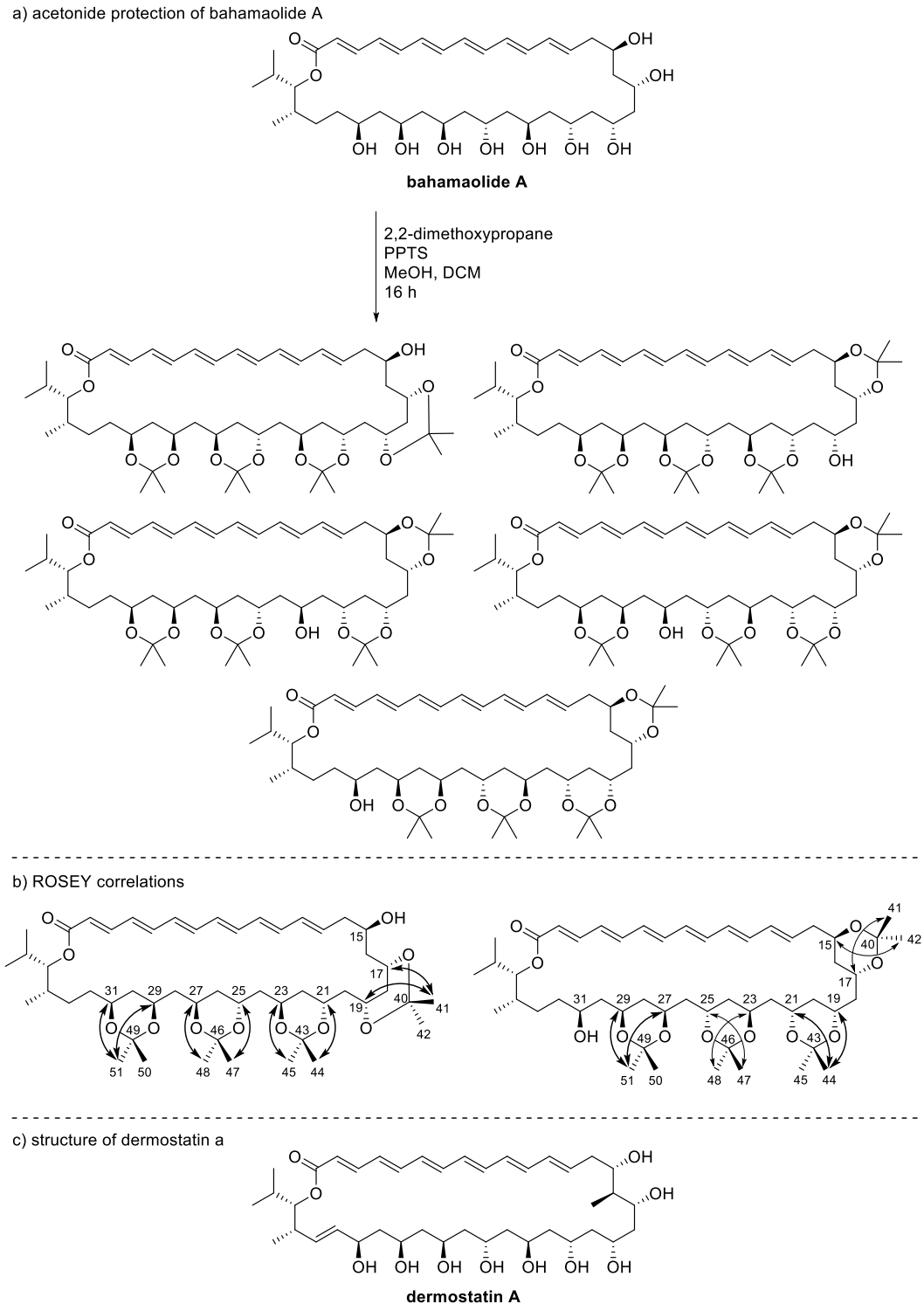


Figure 4 Bahamaolides A and B

The relative configuration of the polyol portion of bahamaolide A was deduced through ^{13}C NMR acetonide analysis (Scheme 94).[2,114] Specifically, treatment of bahamaolide A with an excess of 2,2-dimethoxypropane and PPTS resulted in the formation of the five acetonide protected compounds (Scheme 94a). Analysis of the ^{13}C NMR spectrum of the compound with a free hydroxyl group at the C-15 position suggested the presence of two *syn* acetonides and two *anti* acetonides. The protons at C-17 and C-19 displayed a common ROSEY correlation with the methyl group at C-41, which had a ^{13}C NMR chemical shift of 19.4 ppm which is indicative of the acetonide being in the chair conformation and the C-17 and C-19 hydroxyl groups being *syn* to one another (Scheme 94b). By the same analysis the hydroxyl groups at C-31 and C-29 were also assigned as *syn*. The protons at C-21 and C-23 displayed ROSEY correlations with the methyl groups at C-44 and C-45, respectively, which had ^{13}C NMR chemical shifts of 24.7 ppm and 25.1 ppm, respectively. A HMBC correlation between C-44 and C-45 to C-43 confirmed that the hydroxyl groups at C-21 and C-23 were *anti* to one another. Through the same reasoning the relative configuration between the hydroxyl groups at C-25 and C-27 was

also assigned as *anti*. The same analysis was performed on the compound with a free hydroxyl group at C-31, which showed a *syn* relationship between the hydroxyl groups at C-27 and C-29 and between C-19 and C-21, and an *anti* relationship between the hydroxyl groups at C-23 and C-25 and between C-15 and C-17. Interestingly, the hydroxyl group at C-15 was determined to have the opposite stereochemistry to the hydroxyl group in the same position of the structurally related compound dermostatin A and others, such as roxaticin, and mycoticin (Scheme 94c). This variation highlights the need for the proposed structure to be either confirmed or challenged through total synthesis. The absolute configuration of bahamaolide A was deduced from the compound with a free hydroxyl group at C-31 through Mosher ester analysis.[115]

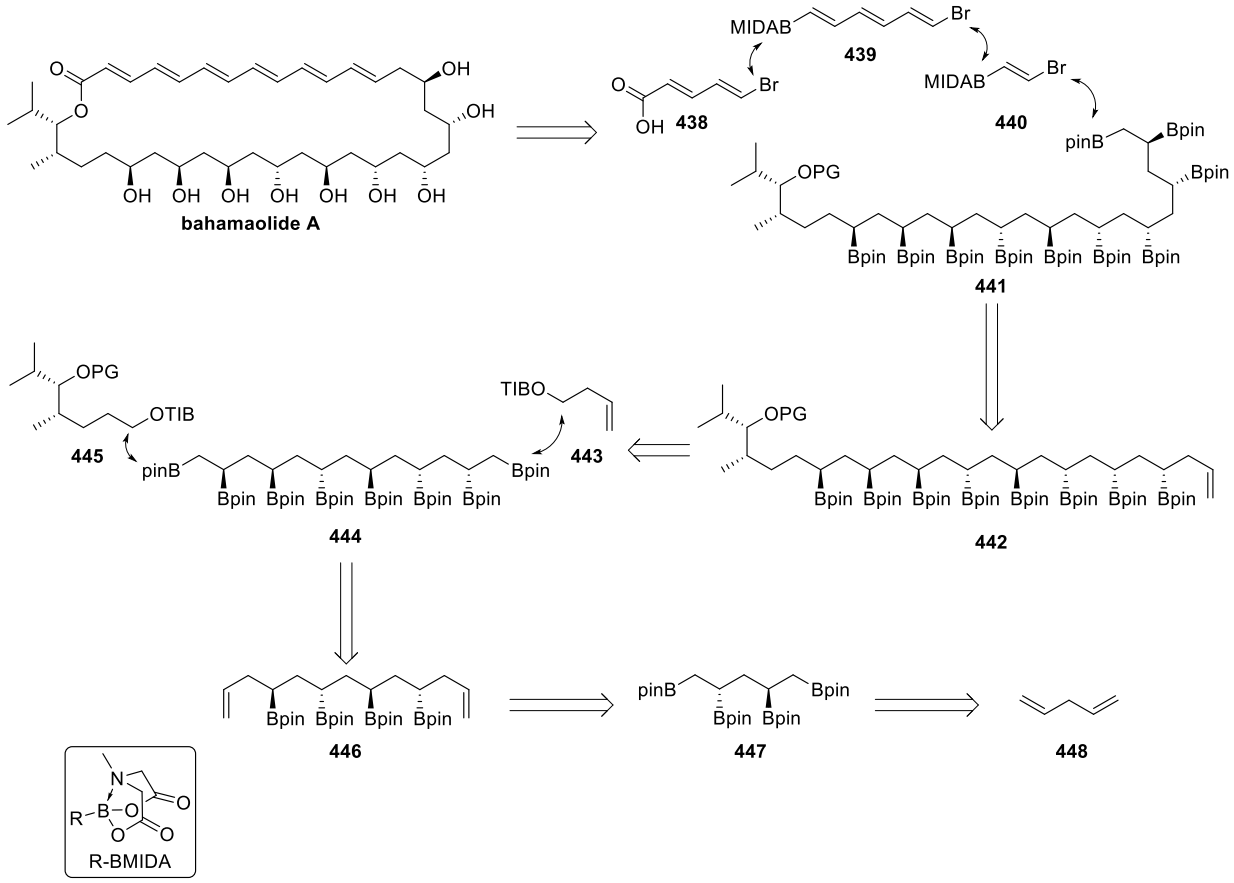


Scheme 94 Bahamaolide A structural elucidation

Retrosynthetic analysis

The C_2-symmetric nature of the 1,3-polyol section of bahamaolide A led us to consider an iterative, bi-directional strategy for its construction. Disconnection of the polyene moiety led to poly(boronic ester) containing fragment **441**, from which each of the stereodefined hydroxyl groups would be revealed through stereospecific oxidation of the

carbon–boron bonds. The polyene unit would be installed through a series of iterative Suzuki reactions using MIDA-protected boronates **440** and **439** and bromide **438** before macrolactonisation would form the macrocycle. Fragment **441** can be simplified to fragment **442** through a diboration reaction, which in turn can be simplified to our key C_2 symmetric octaboronic ester **444** through sequential homologation reactions with carbenoid precursors such as **443** and **445**. Octaboronic ester **444** would be obtained from 1,4-pentadiene (**448**) through an iterative, bi-directional diboration–homologation–diboration sequence going through intermediates **447** and **446**, thus setting six stereogenic centres in just three operations (Scheme 95).



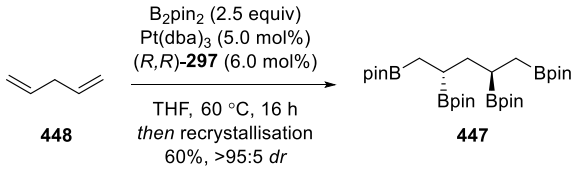
Scheme 95 Retrosynthetic analysis of bahamaolide A

Results and discussion

Previous work

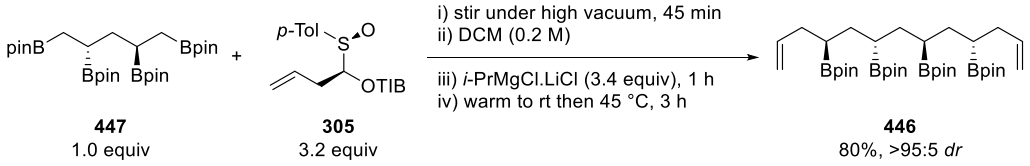
When I accepted to take on this project it had already been worked on by two previous group members – Dr Alexander Fawcett and Dr Teerawut Bootwicha. Dr Fawcett showed the optimisation of the double diboration of 1,4-pentadiene to afford tetraboronic ester **447** in 60% yield and as a single diastereomer after recrystallisation from pentane when

using the diboration conditions described by Morken (Scheme 96).[22,23] He was also the first person to synthesise octaboronic ester **444**.



Scheme 96 Synthesis of tetraboronic ester **447**

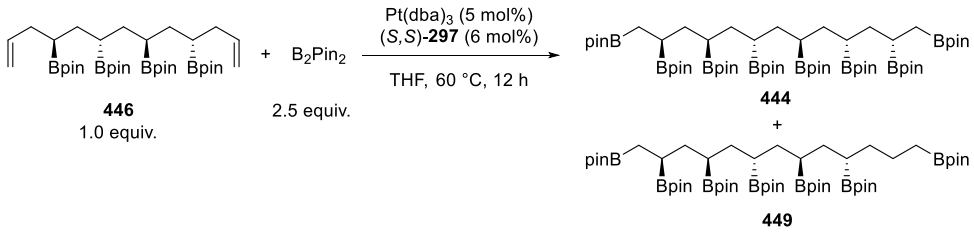
Dr Bootwicha showed the optimisation of the double homologation of tetraboronic ester **447** to afford doubly homoallylic tetraboronic ester **446** and successfully optimised conditions for its purification on a small scale (Scheme 97). Specifically, Dr Bootwicha showed that 3.2 equiv of homoallylic sulfoxide **305**—1.6 equiv per terminal boronic ester—were required, with fewer equivalents giving inferior yields while higher equivalents led to over homologation. As homoallylic sulfoxide **305** co-eluted with homologated tetraboronic ester **446** a slight excess of *i*-PrMgCl·LiCl with respect to **305** was used to ensure complete consumption. Utilization of the corresponding lithium carbenoid—derived through sulfoxide–lithium exchange with *t*-BuLi—gave inferior yields. Purification of **446** was achieved using column chromatography with a mobile phase containing mixtures of hexane, PhMe, DCM and EtOAc and high silica loading. Whilst this method of purification worked well on small scale (ca 50 mg), it proved to be unreliable and non-time efficient with scales in excess of 100 mg.

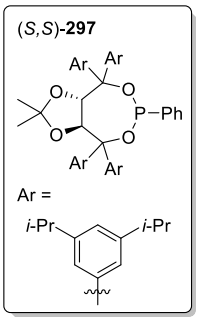


Scheme 97 Synthesis of tetraboronic ester **447**

Dr Bootwicha also showed the optimisation of the double diboration reaction to achieve octaboronic ester **444**. Using the conditions described by Morken, **444** was achieved as a mixture with compound **449**, which arises from a diboration–hydroboration event. **444** and **449** co-elute; however, performing a very difficult column using a mobile phase containing mixtures of hexane, PhMe, DCM, Et_2O and acetone with very high silica loading permitted the isolation of **444** and **449** in 38% and 27% yield, respectively. The amount of **449** formed in the reaction was reduced by performing the reaction at high concentration; specifically, performing the reaction at 1.0 M afforded 64% of octaboronic

ester **444** and only 7% of diboration–hydroboration product **449** (Scheme 98). Unfortunately, the *dr* of **444** could not be determined at this stage by ^{1}H or ^{13}C NMR analysis due to overlapping resonances.





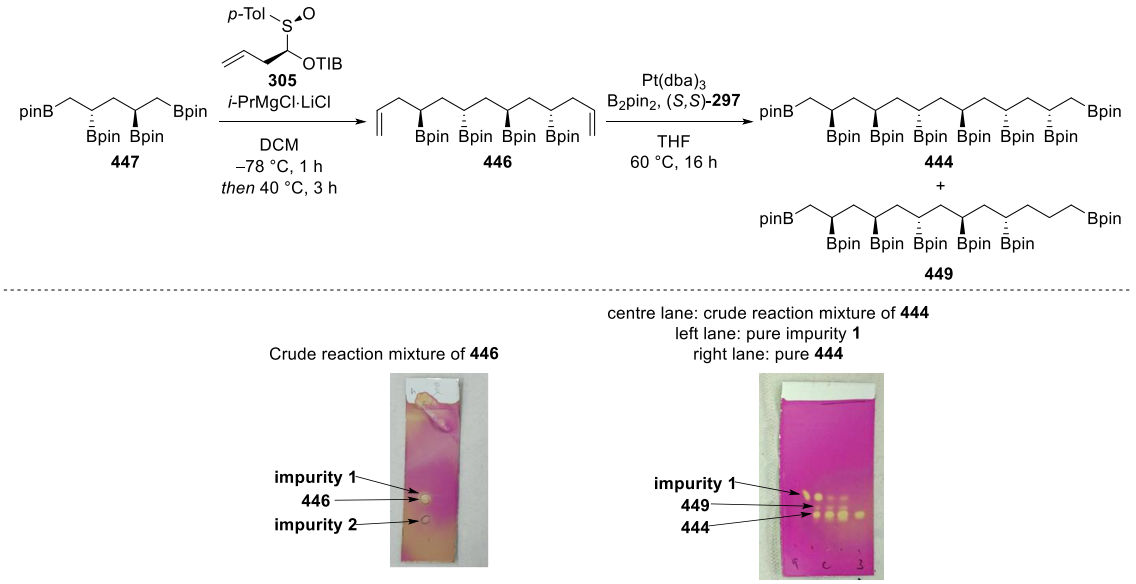
Entry	Reaction concentration / M	Yield **444** / %	Yield **449** / %
1	0.1	38	27
2	1.0	64	7

Scheme 98 Synthesis of octaboronic ester **444**

*Optimisation of the synthesis of octaboronic ester **444***

Although Dr. Bootwicha developed a method to obtain small quantities of very pure octaboronic ester **444**, this required two very challenging and irreproducible columns, which could not supply a sufficient amount of **444** to support a total synthesis project. My first task upon accepting to work on this project was to develop a scalable route to **444** that permitted the formation and isolation of significant quantities of material in a single pass. A thorough re-investigation of TLC solvent conditions for the crude reaction mixture of **446** revealed three spots: the desired product and two impurities, which could not be fully characterised due to overlapping aliphatic resonances in the ^{1}H NMR spectrum (Scheme 99). **Impurity 1** overlapped with the top of the spot corresponding to **446**, whereas **impurity 2** was clearly separated below **446**. Acetone/hexane was the only solvent system identified that could separate all three components. Flash column chromatography using a 5% acetone/hexane mobile phase permitted the separation of **impurity 2**; however, it was not possible to remove **impurity 1** in this way. Fortunately, NMR analysis showed that **impurity 1** did not contain alkenes and so would not interfere in the following asymmetric diboration reaction. The mixture of **446** and **impurity 1** was taken forward to the double diboration reaction. As predicted, **impurity 1** did not influence the reaction and was easily separated from octaboronic ester **444**. The removal of hydroboration product **449** proved to be more of a challenge and could only be distinguished from octaboronic ester **444** by TLC analysis when using acetone/hexane

solvent systems. A mobile phase of 4% acetone/hexane proved to be optimal to separate **444** and **449** using flash column chromatography and allowed 700 mg of octaboronic ester **444** to be isolated following a single purification when the double diboration reaction was performed on a 1.21 mmol scale. The purification of **444** is still a major challenge—each purification takes 6–8 hours to complete and deviating from the standard protocol results in mixed fractions—however, using this method enough material to investigate later stages in the synthesis could be obtained.

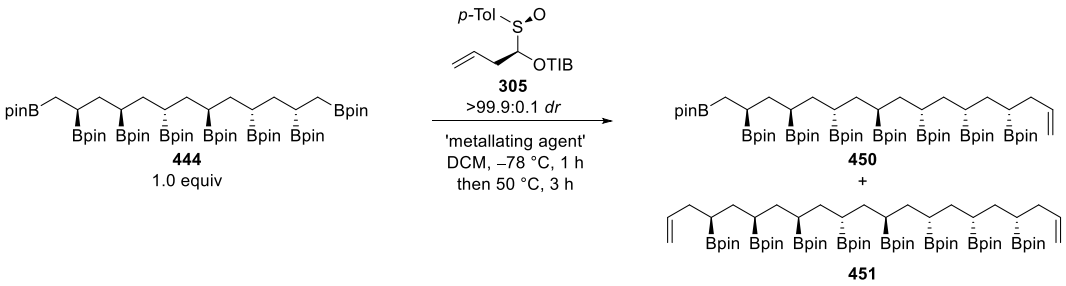


Scheme 99 Synthesis of octaboronic ester **444**

*Desymmetrisation of **444** using α–sulfinyl benzoate **305***

With a method to access octaboronic ester **444** rapidly and on a reasonable scale established, we turned our attention to its desymmetrisation with homoallylic sulfoxide **305**. The desymmetrisation was first attempted by reacting **444** with half the number of equivalents of homoallylic sulfoxide **305** and *i*-PrMgCl·LiCl that were used to homologate tetraboronic ester **447** bi-directionally; specifically, 1.6 equiv of **305** and 1.7 equiv of *i*-PrMgCl·LiCl (Table 3, entry 1). These conditions afforded 23% of the desired desymmetrised product (**450**) along with 14% of over homologated product **451**, with the mass balance being made up with unreacted octaboronic ester **444**. Increasing the number of equivalents of sulfoxide **305** and *i*-PrMgCl·LiCl to 2.0 and 2.1, respectively, gave a modest increase in the yield of **450**, which was afforded in 28% yield along with 14% yield of the over homologated product **451** and returned 52% of octaboronic ester **444** (Table 3, entry 2). Increasing the equivalents further to 2.5 equiv of homoallylic sulfoxide **305** and 2.6 equiv of *i*-PrMgCl·LiCl gave 47% of desymmetrised

octaboronic ester **450**, 31% of over homologated boronic ester **451** and 20% of unreacted octaboronic ester **444** (Table 3, entry 3). The rough 1:2:1 ratio of **451**:**450**:**444** represents a statistical yield for the transformation and was judged to be the maximum yield of **450** that could be obtained when using octaboronic ester **444** as the limiting reagent. We next sought to lower the equivalents of homoallylic sulfoxide **305** by using *t*-BuLi and the sterically demanding triamine PMDTA to perform the metallation, to afford the more reactive lithium carbenoid. Applying the optimal conditions for the homologation of a simple 1,2-bis(boronic ester); specifically, 1.2 equiv of **305**, 1.5 equiv of *t*-BuLi and 1.5 equiv of PMDTA, consumed octaboronic ester **444** but did not afford any of the desired product, and instead showed only a baseline spot by TLC analysis (Table 3, entry 4). This baseline spot could plausibly be caused by direct attack of *t*-BuLi to any one of the boronic ester moieties of **444** to form a non-productive, irreversible *t*-butyl boronate complex, which would sequester **444**. The equivalents of *t*-BuLi with respect to sulfoxide **305** were then adjusted to an equimolar ratio, which permitted the formation of a small amount of the desired desymmetrised product **450** (9%); however, full consumption of **444** was again observed (Table 3, entry 5). Increasing the equivalents of sulfoxide **305** and *t*-BuLi to 1.1 did not positively impact the reaction (Table 3, entry 6) and so entry 3 was selected as the optimal conditions. Presumably, a higher yield of **450** could be obtained by using sulfoxide **305** as limiting reagent and employing a 3–5 equivalent excess of octaboronic ester **444**; however, this was not viewed as an appropriate course of action due to the challenge of accessing **444** and was not investigated. As in the case of octaboronic ester **444**, the purification of desymmetrised octaboronic ester **450** was highly challenging, with the product, **451** and **444** running very close to one another by TLC analysis. After some optimisation it was found that the optimal mobile phase was acetone/PhMe; however, when attempting to purify more than 200 mg of material the purification had to be performed multiple times to recover material from the resulting mixed fractions. Inspection of the allylic resonances in the ^{1}H and ^{13}C NMR spectra suggested that **450** had a *dr* value of >95:5; however, it is plausible that other diastereomers could be concealed by the overlapping resonances in the aliphatic region and so a *dr* value could not be confidently reported at this stage.



Entry	Equivalents of **305**	Metallation conditions	Solvent	Yield of **450** / %	Yield of **451** / %	Recovered **444** / %
1	1.6	*i*-PrMgCl·LiCl (1.7 equiv)	DCM	23	14	60
2	2.0	*i*-PrMgCl·LiCl (2.1 equiv)	DCM	28	14	52
3	2.5	*i*-PrMgCl·LiCl (2.6 equiv)	DCM	47	31	20
4	1.2	*t*-BuLi (1.5 equiv) PMDTA (1.5 equiv)	THF	0	0	0
5	1.0	*t*-BuLi (1.0 equiv) PMDTA (1.1 equiv)	THF	9	0	0
6	1.1	*t*-BuLi (1.1 equiv) PMDTA (1.2 equiv)	THF	8	0	0

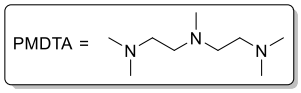
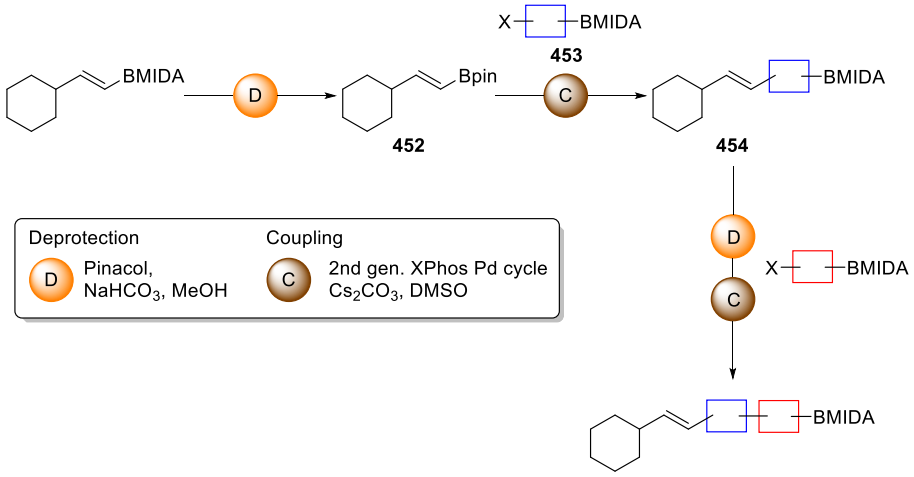


Table 3 Desymmetrisation of octaboronic ester **444** with homoallylic sulfoxide **305**

While investigating conditions for the desymmetrisation of octaboronic ester **444**, model studies towards the construction of the polyene moiety were conducted concurrently and will be discussed in the next section.

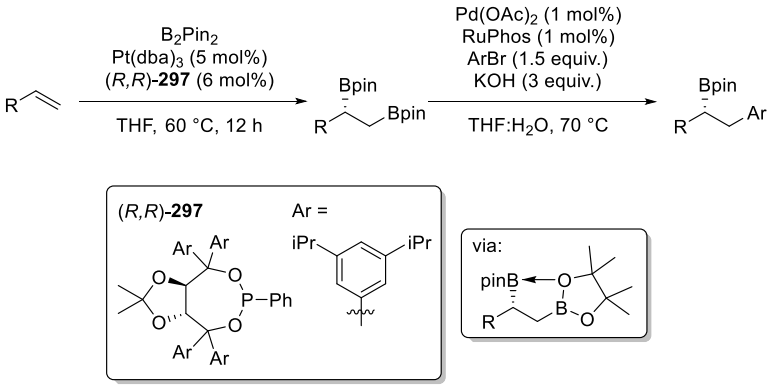
Investigation of an iterative Suzuki-coupling strategy for the synthesis of the polyene

To install the polyene moiety, we aimed to use an iterative Suzuki coupling strategy using MIDA boronates, which was pioneered by Burke (Scheme 100).[116] Specifically, Suzuki coupling reactions between a vinyl pinacol boronic ester, such as **452**, and a bi-functional coupling partner **453** containing a MIDA boronate proceeded to give a single product when performed under anhydrous conditions using Buchwald's second generation XPhos Pd cycle precatalyst,[117] Cs_2CO_3 and DMSO. Deprotection of MIDA boronate **454** under basic conditions in the presence of pinacol generated a reactive pinacol boronic ester, which was primed to undergo a further Suzuki coupling reaction. This procedure was performed iteratively to build molecular complexity in a modular fashion one unit at a time.



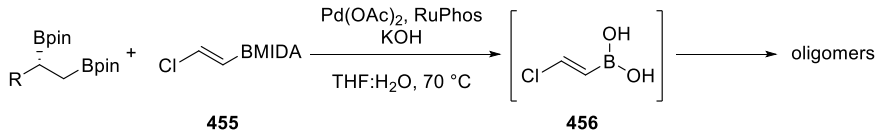
Scheme 100 Burke's iterative Suzuki approach utilizing MIDA boronates

Morken has shown that 1,2-bis(boronic esters) undergo selective Suzuki coupling reactions at the primary boronic ester with aryl bromide or vinyl chloride electrophiles in yields typically greater than 90% when using $Pd(OAc)_2$, RuPhos and KOH as base (Scheme 101).[118] Interestingly, simple primary boronic esters do not react under these conditions and it was proposed that internal chelation of the primary boronic ester pinacol group to the secondary boron centre increases the Lewis acidity of the terminal boronic ester and thus accelerates transmetallation at this position.



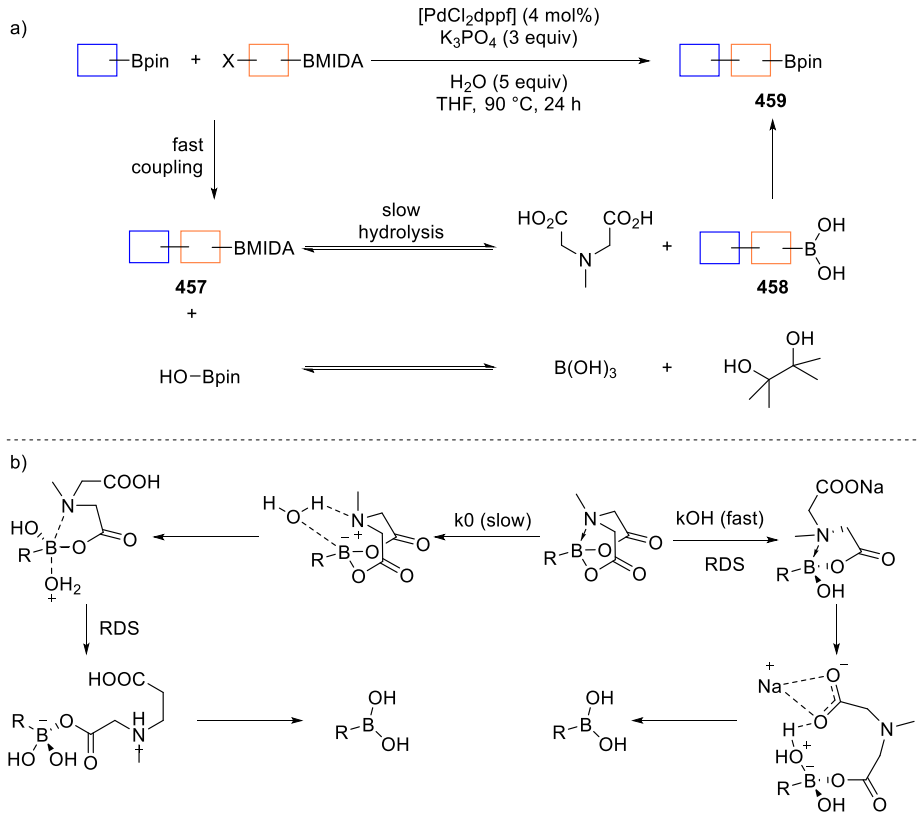
Scheme 101 Morken's primary selective Suzuki coupling of 1,2-bis(boronic esters) with aryl bromides

Unfortunately, Morken and Burke's methodologies are incompatible as the strong aqueous base required for Morken's coupling would prematurely deprotect MIDA boronate **455** to reveal boronic acid **456**, which would react non-selectively to generate a mixture of oligomeric products (Scheme 102).



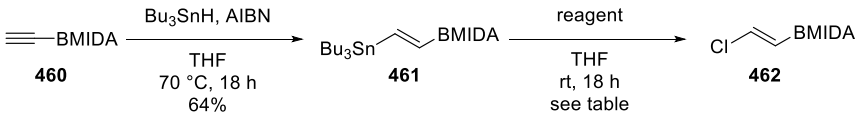
Scheme 102 Incompatibility between Morken and Burke's cross-coupling methodologies

The Watson group have shown that weaker aqueous bases; specifically, K_3PO_4, can be used in Suzuki reactions employing MIDA-protected building blocks without the formation of oligomeric products (Scheme 103a).[119–122] Termed 'boron speciation', Watson's methodology relies on a rapid coupling event—that typically occurs within the first hour of the reaction—to generate a homologated MIDA boronate, such as **457**. The aqueous K_3PO_4 then slowly hydrolyses the MIDA boronate to liberate the corresponding boronic acid (**458**), which is esterified with pinacol present in the reaction mixture to generate boronic ester **459**. Burke and Lloyd-Jones have shown that hydrolysis of MIDA boronates occurs through different mechanisms depending on whether NaOH or K_3PO_4 is used as the base (Scheme 103b).[123] When using NaOH fast hydrolysis occurred, where the rate determining step is attack by a single hydroxide. Typically, these fast processes take minutes to unveil the boronic acids at ambient temperature. Conversely, utilisation of K_3PO_4 resulted in a slow hydrolysis in which the rate determining step is the attack of water clusters.



Scheme 103 Watson's boron speciation and hydrolysis mechanisms of MIDA boronates

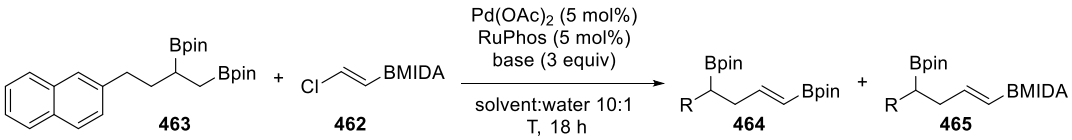
We sought to merge the methodologies of Morken, Burke and Watson to install the polyene moiety of bahamaolide A. Interestingly, Morken reported that whilst aryl bromide electrophiles reacted in high yields in cross-coupling reactions with 1,2-bis(boronic esters), vinyl bromides and iodides were poor reaction partners and that vinyl chlorides had to be utilised for high yields. The synthesis of MIDA boronate containing vinyl chloride **462** was achieved as shown in Table 4. Radical stannylation of alkynyl MIDA boronate **460** proceeded to furnish MIDA boronate **461**. Conversion of **461** to vinyl chloride **462** did not proceed upon stirring with NCS overnight (Table 4, entry 1); however, using Cu(II)Cl as the chlorinating agent resulted in clean formation of **462**, albeit in low yield (Table 4, entry 2). Compound **462** proved to be highly hydrophilic and modification of the work up procedure to remove the aqueous work up resulted in a much improved yield (Table 4, entry 3).



Entry	Reagent	Comment	Yield / %
1	NCS	no conversion (TLC)	0
2	Cu(II)Cl	aqueous work up	22
3	Cu(II)Cl	no aqueous w/u	82

Table 4 Synthesis of vinyl chloride **462**

With the required vinyl chloride in hand, we next investigated the cross coupling reaction with model 1,2-bis(boronic ester) **463**. It was anticipated that either **464** or **465**, or a mixture of both would be obtained depending on the efficiency of MIDA boronate hydrolysis. As expected, subjection of **462** and **463** to the conditions described by Morken; specifically, 70 °C overnight using NaOH as base, resulted in a complex mixture, presumably through premature deprotection of the MIDA boronate and subsequent oligomerisation (Table 5, entry 1). A modest screen of bases was then performed. Using K_3PO_4 alleviated the putative oligomerisation of MIDA boronate **463** but no reactivity was observed, as determined by LCMS analysis, and both **462** and **463** were recovered (Table 5, entry 2). Performing the reaction with Cs_2CO_3, K_2CO_3 or NEt_3 (Table 5, entries 3 – 5) provided no improvement – again no reactivity was observed by LCMS analysis and the starting materials were recovered. The solvent was then changed to DMSO to be in line with Burke's procedure (Table 5, entries 6 – 9); however, the same result was observed. Furthermore, the lack of reactivity could not be improved by performing the reaction at 90 °C in either THF or DMSO (Table 5, entries 10 – 17), which again returned the starting materials unchanged.



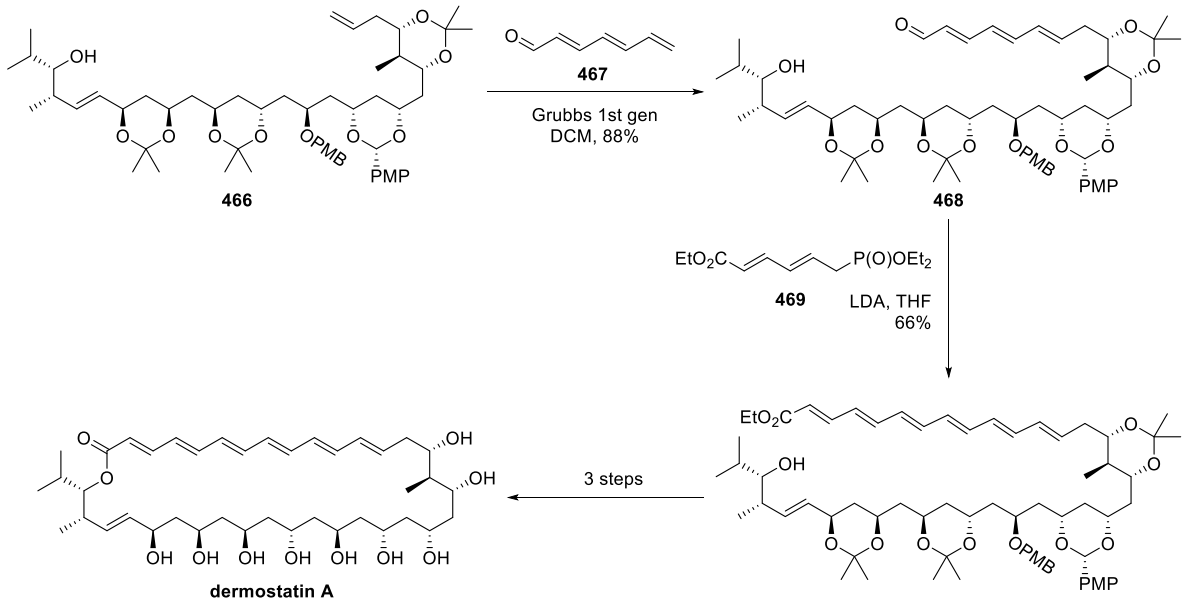
Entry	Base	T / °C	Solvent	Result
1	NaOH	70	THF	complex mixture of products
2	K_3PO_4	70	THF	starting materials recovered
3	Cs_2CO_3	70	THF	starting materials recovered
4	K_2CO_3	70	THF	starting materials recovered
5	NEt_3	70	THF	starting materials recovered
6	K_3PO_4	70	DMSO	starting materials recovered
7	Cs_2CO_3	70	DMSO	starting materials recovered
8	K_2CO_3	70	DMSO	starting materials recovered
9	NEt_3	70	DMSO	starting materials recovered
10	K_3PO_4	90	THF	starting materials recovered
11	Cs_2CO_3	90	THF	starting materials recovered
12	K_2CO_3	90	THF	starting materials recovered
13	NEt_3	90	THF	starting materials recovered
14	K_3PO_4	90	DMSO	starting materials recovered
15	Cs_2CO_3	90	DMSO	starting materials recovered
16	K_2CO_3	90	DMSO	starting materials recovered
17	NEt_3	90	DMSO	starting materials recovered

Table 5 Attempted cross-coupling reaction between vinyl chloride **462** and 1,2-bis(boronic ester) **463**

Due to the lack of reactivity between vinyl chloride **462** and bis(boronic ester) **463** under the tested reaction conditions, the iterative Suzuki strategy was abandoned in favour of a more promising approach.

Sammakia's strategy for the synthesis of the polyene portion of RK397 and dermostatin A

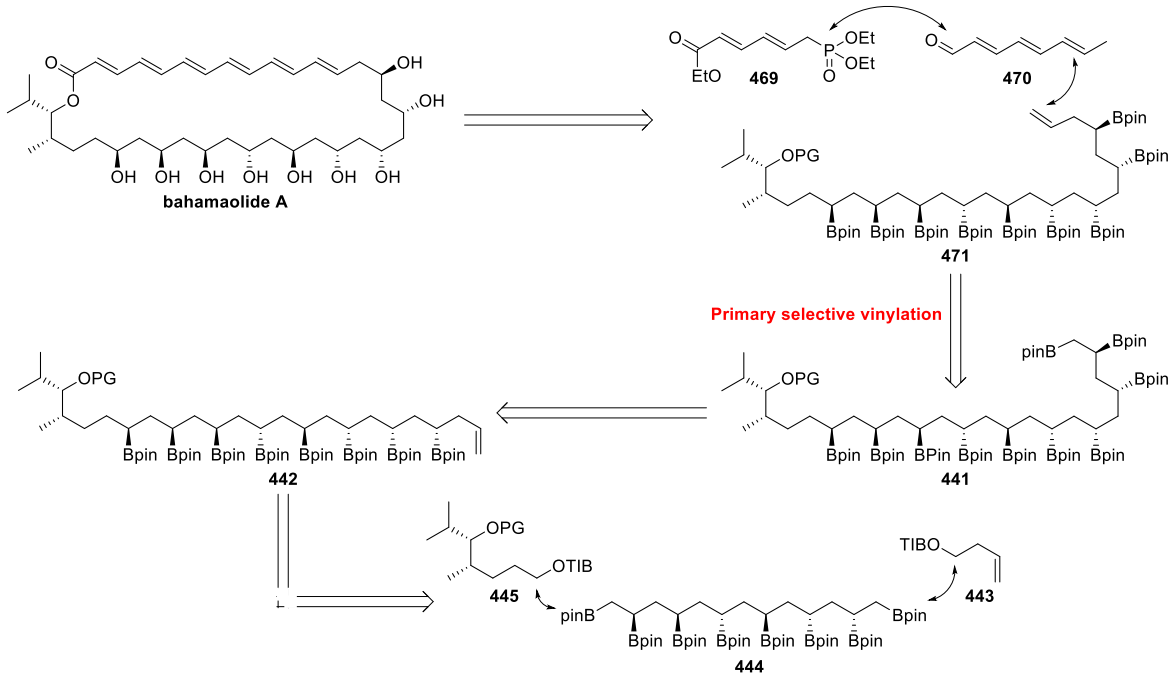
As an alternative method to synthesise the polyene region of bahamaolide A, we were drawn to a strategy pioneered by Sammakia in his syntheses of RK397[124] and dermostatin A,[125] which utilised a cross metathesis reaction between advanced polyol containing fragment **466** and conjugated aldehyde **467** to afford trienal **468**. The remaining alkenes were installed through a Horner-Wadsworth-Emmons (HWE) reaction with phosphonate **469** to yield an advanced intermediate that was converted to dermostatin A in a further three steps; specifically, ester saponification, macrolaconisation and global deprotection (Scheme 104).



Scheme 104 Sammakia's approach towards the synthesis of the polyene region of dermostatin A

Retrosynthetic analysis version 2.0

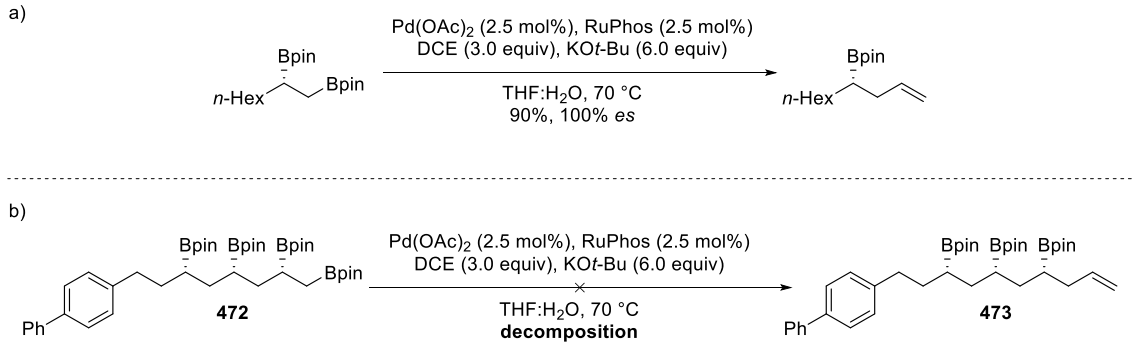
The advantage of this method was that the required homoallylic alkene could potentially be accessed through a primary selective vinylation reaction of poly(boronic ester) containing intermediate **441**. The retrosynthetic analysis of bahamaolide A was therefore altered to install the polyene moiety using Sammakia's strategy (Scheme 105). Disconnection of the polyene moiety revealed advanced poly(boronic ester) containing intermediate **471**, which would be accessed from **441** through a selective vinylation reaction of the primary boronic ester. **441** would be accessed in the same manner previously described from octaboronic ester **44** through sequential homologation reactions with carbenoid precursors such as **443** and **445** to generate **442**, which would undergo a diboration reaction at the pendant olefin.



Scheme 105 Second generation retrosynthetic analysis of bahamaolide A

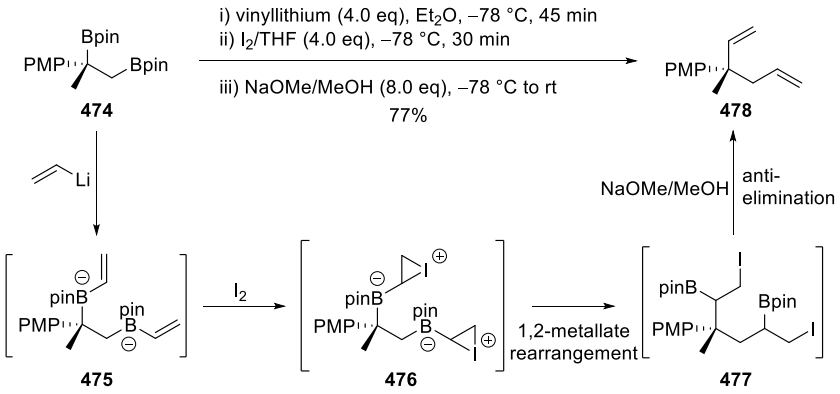
Development of a primary selective vinylation of 1,2-bis(boronic esters)

We next turned our attention to identifying a selective vinylation reaction of the primary boron moiety of a 1,2-bis(boronic ester). Morken has shown a palladium catalysed cross-coupling reaction between the primary boronic ester of a 1,2-bis(boronic ester) and vinyl chloride,[118] which was generated *in situ* through elimination of dichloroethane with KO*t*-Bu (Scheme 106a). When applying these conditions to poly(boronic ester) **472** the desired product **473** was not obtained (Scheme 106b). Instead, complete conversion of the starting materials to a baseline spot was observed by TLC analysis, which suggested decomposition. It is hard to rationalise why decomposition of **472** would occur; however, after obtaining the same result after multiple repeats of the reaction, this approach was abandoned.



Scheme 106 Morken's primary selective vinylation of a 1,2-bis(boronic ester) and our attempt to emulate it using poly(boronic ester) **472** as the substrate

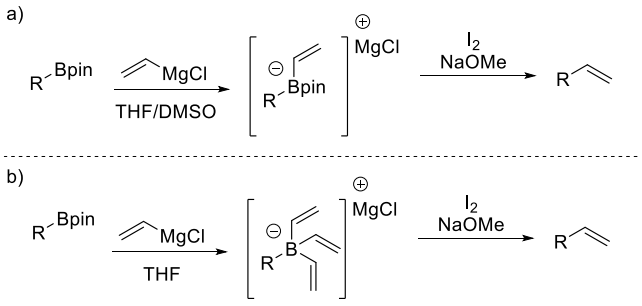
Aggarwal has shown that 1,2-bis(boronic esters) react in a Zweifel olefination reaction at both boron centres to generate bis(functionalised) products when an excess of reagents are used (Scheme 107).[126] Specifically, addition of vinyllithium—generated from the tin–lithium exchange of tetravinyl tin with *n*-BuLi—to both boron centres of bis(boronic ester) **474** afforded bis(vinyl boronate complex) **475**. Treatment of **475** with I_2 furnished bis(iodonium) **476**, which underwent 1,2-metallate rearrangement to give homologated bis(boronic ester) **477**. Anti-elimination of **477** after the addition of NaOMe/MeOH ensued to furnish bis(alkene) **478** in high yield.



Scheme 107 Bis(vinylation) of a 1,2-bis(boronic ester)

We sought to adapt these conditions to enable a primary selective vinylation reaction of 1,2-bis(boronic esters) using the mechanistic manifold of the Zweifel olefination reaction. We envisaged that exclusive formation of a boronate complex at the primary boronic ester could be achieved by carefully controlling the stoichiometry of the reaction as well as employing sterically hindered di- or tri-amine ligands to sequester the reactivity of vinyl lithium. Because this procedure would ultimately be used on a substrate that contains 9 secondary boronic esters, the threshold for what was considered to be an acceptable level of bis(functionalisation) in a simple bis(boronic ester) was set to 0%. In an initial attempt, model bis(boronic ester) **479** was reacted with 1.0 equiv of vinyl lithium in the presence of 1.1 equiv of PMDTA at –78 °C. The putative boronate complex was then treated successively with I_2 and NaOMe. These conditions led to 13% yield of the desired product **480**; however, the major species obtained was bis(functionalised) product **481**, which was isolated in 45% yield (Table 6, entry 1). The predominance of **481** led us to search for a less reactive vinyl nucleophile. Aggarwal has shown that vinyl boronate complexes can be achieved by adding vinylmagnesium chloride to boronic esters using a 1:1 mixture of THF/DMSO as solvent (Scheme 108a).[127] In the absence of DMSO a trivinylboronate

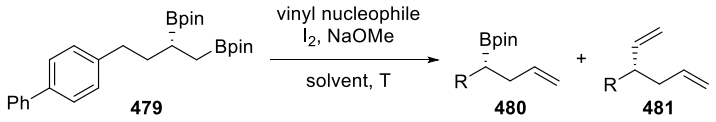
complex, which arises through displacement of the pinacol group by 3.0 equiv of vinylmagnesium chloride, was observed exclusively. The trivinylboronate complex was a productive intermediate in the transformation; however, it was preferable to use 1.0 equiv of vinylMgCl in order to reduce waste and avoid potential functional group incompatibility (Scheme 108b).



Scheme 108 Aggarwal's modified Zweifel olefination

Utilization of 1.2 equiv of vinylmagnesium chloride in a 1:1 mixture of THF/DMSO at 0 °C with **479** afforded only 10% of the desired product **480**, with the mass balance being made up with unreacted starting material and a trace amount of bis(functionalised) product **481** (Table 6, entry 2). Instead of increasing the equivalents of vinylmagnesium chloride, which would presumably also increase the amount of over-homologation, we initially opted to increase the reactivity of the vinyl nucleophile. Knochel has shown that the reactivity of Grignard reagents towards magnesium–halogen exchange reactions increases in the presence of LiCl.[128] Moreover, Morken has shown that formation of boronate complexes with vinylmagnesium chloride was enhanced when using LiCl as an additive.[129] The reaction was then repeated using 1.6 equiv of vinylmagnesium chloride and a 0.5 M solution of LiCl in THF in a 1:1 mixture with DMSO as solvent (Table 6, entry 3). Under these conditions poor consumption of the starting material was still observed and bis(functionalised) product **481** was isolated in 24% yield while the desired product **480** was only obtained in 7.5% yield. We then investigated the effect of changing the equivalents of vinylmagnesium chloride; however, performing the reaction with 2.0 and 3.0 equiv of vinylmagnesium chloride only served to increase the amount of bis(functionalisation), as expected (43% and 65% yield, respectively, Table 6, entries 4 and 5). Performing the reaction at –78 °C in THF with 1.5 equiv of vinylmagnesium chloride afforded similar yields of **480** and **481**, with the mass balance being made up with unreacted starting material. Finally, we attempted to use bulky amine ligands to disfavour formation of a boronate complex at the more hindered secondary boronic ester

moiety. Surprisingly, this resulted in the complete arrest of the reaction and permitted the recovery of 80% of **479** in the case of PMDTA and 78% of **479** in the case of (+)-sparteine (Table 6, entries 7 and 8). Due to the unfavourable results from this model study, we abandoned this approach to pursue a more promising one using lithiation–borylation reactions.



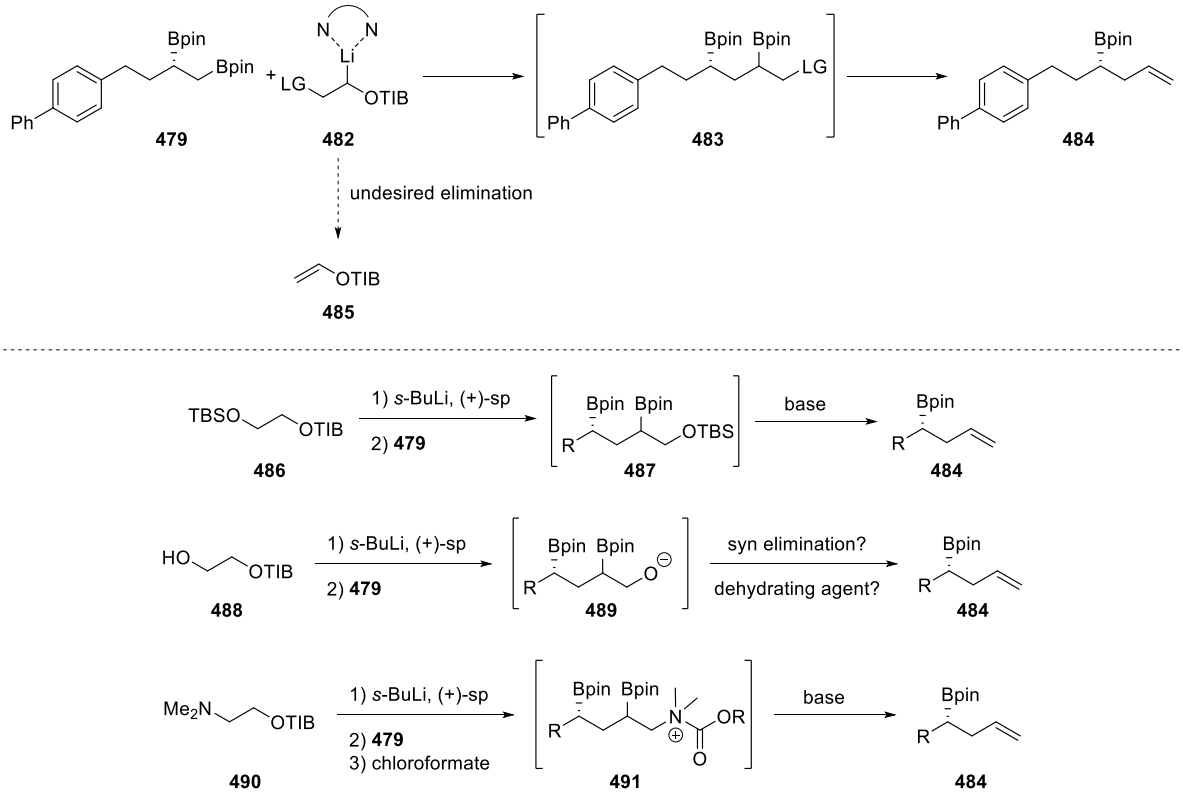
479 **480** **481**

Entry	Vinyl nucleophile	Diamine	I_2 equiv	NaOMe equiv	Solvent	T / °C	Yield **480** / %	Yield **481** / %	Recovered **479** / %
1	 1.00	PMDTA 1.10	4.00	8.00	THF	–78	13	45	0
2	 1.20	—	1.20	3.00	THF/ DMSO	0	10	3	85
3	1.60	—	1.60	3.00	THF·LiCl/ DMSO	0	7.5	24	37
4	2.00	—	2.00	3.00	THF/ DMSO	0	18	43	4
5	3.00	—	3.00	3.00	THF/ DMSO	0	13	65	0
6	1.50	—	1.60	3.00	THF	–78	13	14	61
7	2.00	PMDTA 2.00	2.00	3.00	THF/ DMSO	0	3	0	80
8	2.00	(+)-sp 2.00	2.00	3.00	THF/ DMSO	0	4	0	78

Table 6 Vinylation of 1,2-bis(boronic ester) **479**

As it is known that (+)-sparteine coordinated lithiated benzoates react selectively at the primary position of a 1,2-bis(boronic ester),[83] we next attempted to develop a primary selective vinylation reaction of a 1,2-bis(boronic ester) by employing a lithiated benzoate with a β-leaving group, such as **482** (Scheme 109). Treatment of a 1,2-bis(boronic ester) with **482** would lead to an intermediate such as **483**, which could undergo an elimination reaction to yield the desired product. However, lithiated benzoates with β-leaving groups

are known to be chemically unstable and eliminate prematurely to furnish vinyl benzoate (**485**). To avoid this premature elimination reaction, a masked leaving group would have to be used, i.e. one that cannot leave before being activated with a suitable reagent. With these criteria established, we selected benzoates **486**, **488** and **490** as viable candidates. In the case of benzoate **486**, reaction with bis(boronic ester) **479** would deliver intermediate 1,3-bis(boronic ester) **487**, which should undergo anti-elimination after addition of a base. Lithiation of hydroxyl benzoate **488** with two equivalents of *s*-BuLi should form a dianion, where the hydroxyl group has been protected as its conjugate base, which will react with **479** to generate intermediate **489**. Optimally, a spontaneous syn-elimination would furnish homoallylic boronic ester **484**; however, if this operation does not occur a dehydrating agent could be added to promote the elimination. Finally, formation of a boronate complex between the carbenoid derived from benzoate **490** and **479** would generate a 1,3-bis(boronic ester) such as **491**. The tertiary amine of **491** could be activated with a chloroformate to afford an activated carbamate, which could undergo elimination upon addition of a base.[130]

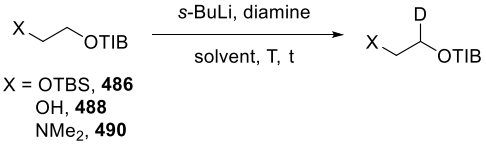


Scheme 109 Proposed primary selective vinylation reaction of 1,2-bis(boronic esters) using lithiated benzoates with β-leaving groups

The efficiency of the lithiation of **486**, **488**, and **490** was first evaluated using a lithiation–deuteration study (Table 7). Treatment of benzoate **486** with 1.3 equiv of

s-BuLi and TMEDA for 3 h followed by quenching with CD_3OD did not give deuterium incorporation at the desired position, but gave complete conversion to vinyl benzoate (**485**), thus confirming that **486** is not a suitable carbenoid precursor (Table 7, entry 1). Lithiation of hydroxyl benzoate **488** for 3 h using 2.3 equiv of *s*-BuLi and TMEDA followed by quenching with CD_3OD afforded 100% deuterium incorporation of the hydroxy group but no deuterium incorporation at the desired position (Table 7, entry 2). Performing the reaction with (+)-sparteine in place of TMEDA also did not permit deuterium incorporation at the position α to the benzoate (Table 7, entry 3). Aggarwal has shown that the recalcitrant lithiation of secondary dialkylbenzoates can be achieved when using an excess of TMEDA with respect to *s*-BuLi and by using CPME as solvent;[43] however, subjection of **488** to 2.3 equiv of *s*-BuLi and 8.6 equiv of TMEDA in CPME at –78 °C resulted in only 20% deuterium incorporation at the desired position after addition of CD_3OD (Table 7, entry 4). Our attention then turned to tertiary amine containing benzoate **490**. Beak has shown that deuterated **490** can be obtained in 82% yield from **490** by lithiating with *s*-BuLi/TMEDA at −78 °C in THF.[131] In our hands, subjecting **490** to 1.3 equiv of *s*-BuLi and TMEDA for 1 h at −78 °C resulted in 100% deuterium incorporation after quenching with CD_3OD; however, only 72% yield was isolated due to non-specific decomposition of **490** under the reaction conditions (Table 7, entry 5). It has been shown that using THF as solvent leads to poor *ee* values in sparteine mediated enantioselective deprotonation reactions;[132] moreover, THF is an inferior solvent to Et_2O in the stereospecific deprotonation of secondary dialkylbenzoates.[130] Both of these observations suggest deleterious attributes surrounding the use of THF and so the reaction was repeated using Et_2O as solvent. Treatment of **490** with 1.3 equiv of *s*-BuLi and (+)-sparteine at −78 °C for 3 h in Et_2O again afforded 100% deuterium incorporation after addition of CD_3OD, but only 56% of the deuterated compound was isolated (Table 7, entry 6). To reduce the amount of decomposition the lithiation time was reduced. Performing the reaction for 30 min furnished 87% deuterium incorporation but decomposition was prevalent when inspecting the crude ^1H NMR spectrum (Table 7, entry 7). Further decreasing the lithiation period to 10 min resulted in a comparable deuterium incorporation value (84%) but decomposition was persistent (Table 7, entry 8). Finally, the lithiation was performed at −100 °C for 1 h, which did not improve deuterium incorporation or suppress decomposition as determined by crude ^1H NMR analysis (Table 7, entry 9). With these disappointing results in hand, we elected to adopt

a new approach to install the homoallyl group through a lithiation−borylation reaction using carbenoid precursor **495** (Scheme 111).

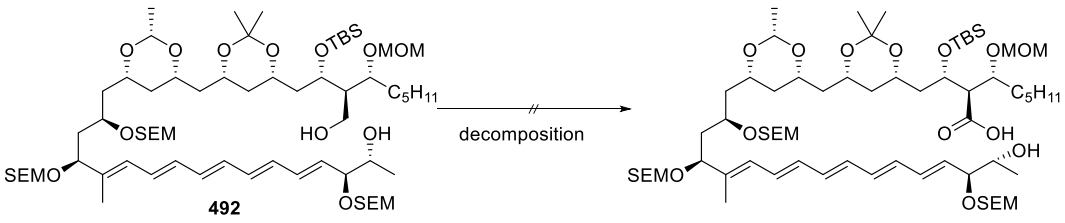


Entry	Carbenoid precursor	*s*-BuLi / equiv	Diamine / equiv	Solvent	T / °C	t / hr	D incorp. / %	isolated yield / %
1	**486**	1.3	TMEDA / 1.3	Et_2O	–78	3	0 decomposition to vinyl benzoate	–
2	**488**	2.3	TMEDA / 2.3	Et_2O	–78	3	100 - hydroxyl 0 - desired position	–
3	**488**	2.3	(+)-sp / 2.3	THF	–78	3	100 - hydroxyl 0 - desired position	–
4	**488**	2.3	TMEDA / 8.6	CPME	–50	3	100 - hydroxy 20 - desired position	–
5	**490**	1.3	TMEDA / 1.3	THF	–78	1	100	72
6	**490**	1.3	(+)-sp / 1.3	Et_2O	–78	3	100	56
7	**490**	1.3	(+)-sp / 1.3	Et_2O	–78	0.5	87	–
8	**490**	1.3	(+)-sp / 1.3	Et_2O	–78	0.17	84	–
9	**490**	1.3	(+)-sp / 1.3	Et_2O	–95	1	78	–

Table 7 Lithiation–deuteration studies of benzoates **486**, **488** and **490**

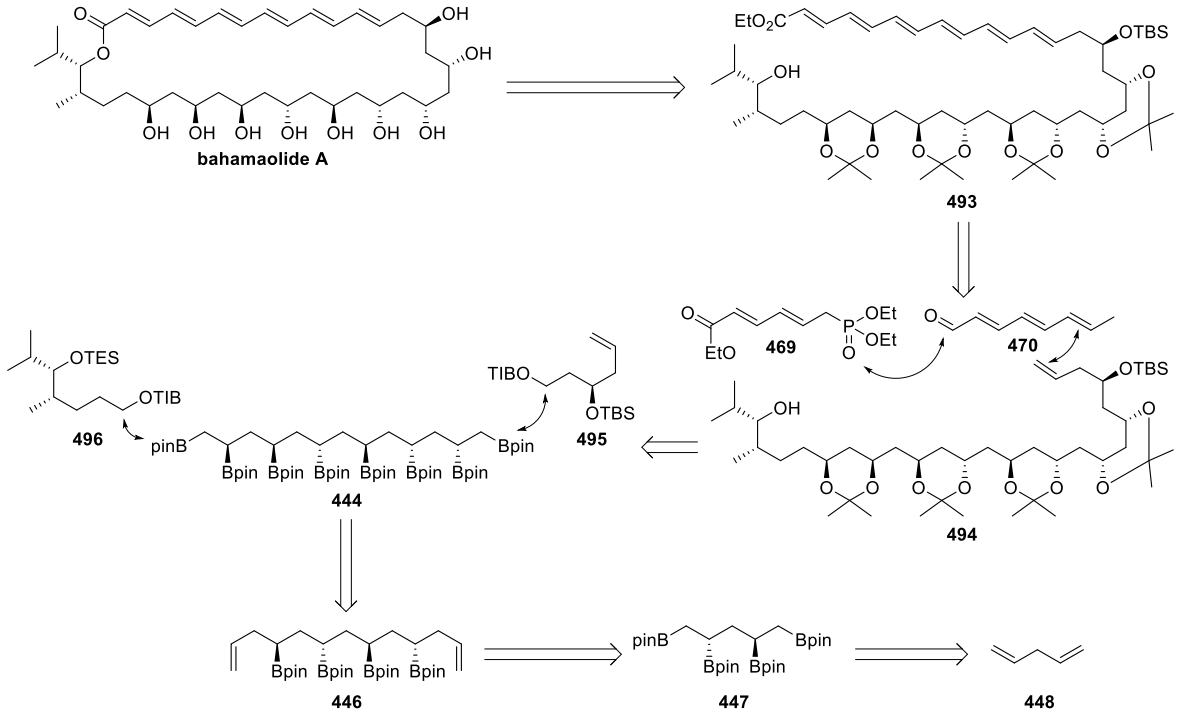
Retrosynthetic analysis version 3.0

The difficulty that we experienced in developing a primary selective vinylation of 1,2-bis(boronic esters) led us to consider installing the homoallyl group through a lithiation−borylation reaction with carbenoid precursor **495** (Scheme 111). We also decided to perform the oxidation of the boronic esters before the installation of the polyene because Cossy has shown that the polyene moiety of **492** is unstable to oxidising conditions (Scheme 110).[133]



Scheme 110 Decomposition of **492** under oxidising conditions

The retrosynthetic analysis was altered to reveal acetonide protected polyol **493**, which would be obtained from polyol **494** through a metathesis reaction with trienal **470** and a HWE reaction with phosphonate **469**. **494** leads back to octaboronic ester **444** through sequential homologation reactions with carbenoid precursors **495** and **496** and oxidation of the resulting (poly)boronic ester containing compound (Scheme 111).

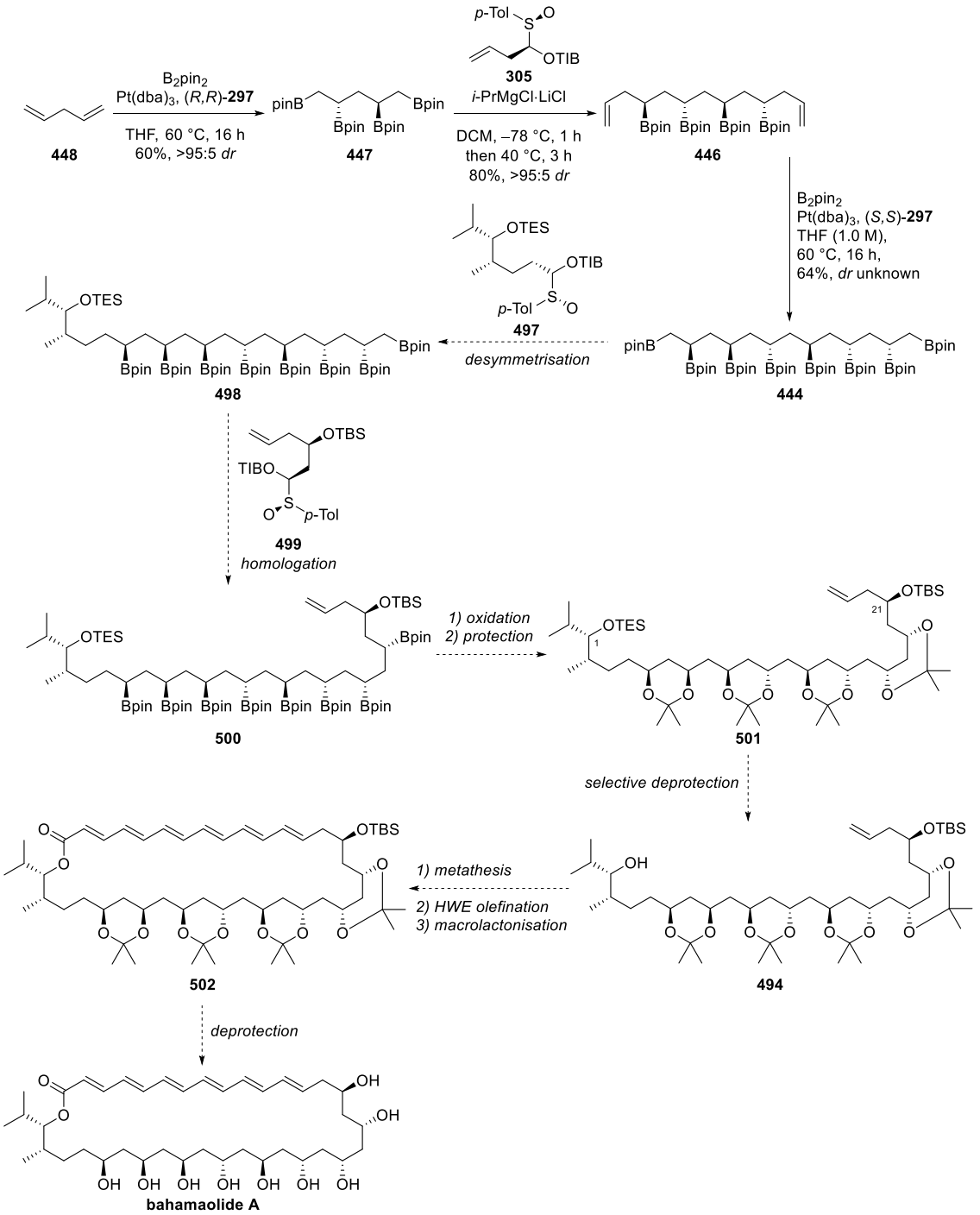


Scheme 111 Retrosynthetic analysis of bahamaolide A

Proposed forward synthesis of bahamaolide A

As described previously, the forward synthesis would commence with the synthesis of octaboronic ester **444** through the diboration–homologation–diboration sequence from 1,4-pentadiene (**448**) (Scheme 112). Desymmetrisation of **444** would now be performed with sulfoxide **497** to afford homologated poly(boronic ester) **498**. Installation of the pendant alkene required for the metathesis reaction with trienal **470** would be achieved through homologation of the primary boronic ester moiety of **498** with sulfoxide **499** to generate **500**. Stereospecific oxidation of all eight boronic esters would yield a poly(alcohol), which would be protected as the poly(acetonide) to yield **501**. The use of different silyl ether protecting groups in sulfoxides **497** and **499** is necessary because Krische has shown that the hydroxy group at C-21 must be protected for macrolactonisation to be successful;[113] whereas, Sammakia reported the metathesis–HWE–macrolactonisation sequence when the hydroxyl group at C-1 was unprotected.[124,125] Selective deprotection of the more labile TES silyl ether at the C-1

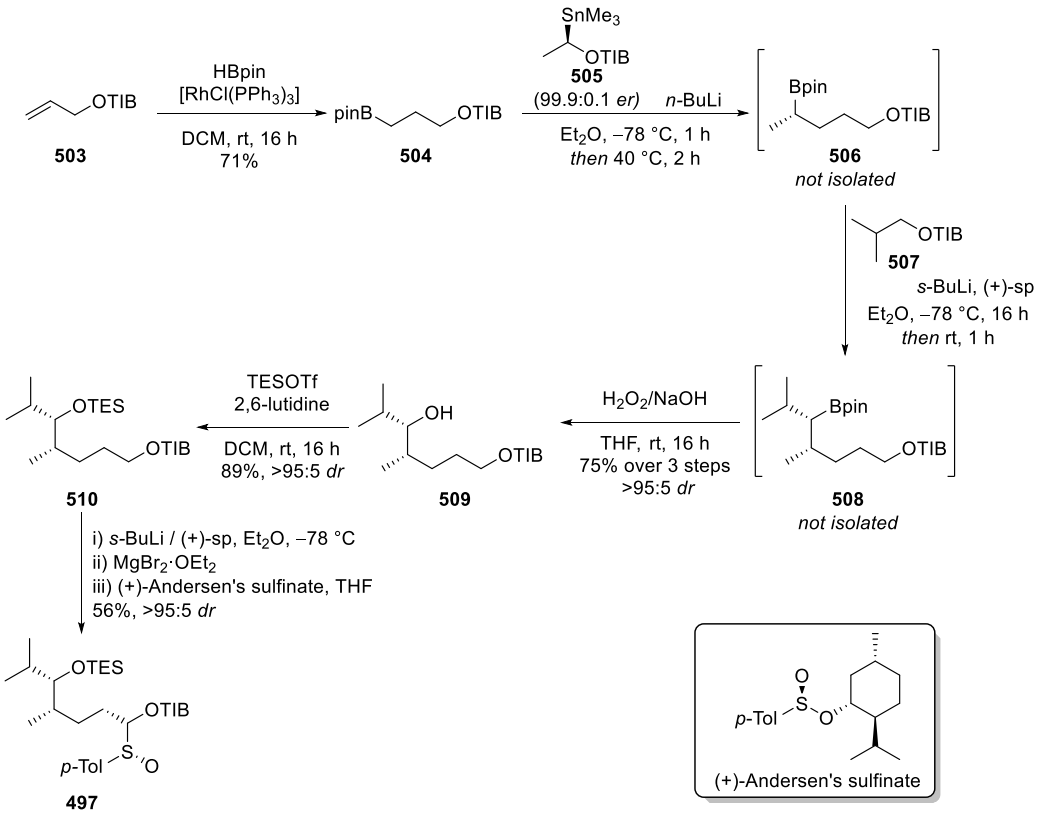
position in the presence of the TBS silyl ether at the C-21 position would afford alcohol **494**, which is primed to undergo the methathesis–HWE–macrolactonisation sequence to generate protected bahamaolide A (**502**). Global deprotection under acidic conditions would afford the desired natural product and conclude the total synthesis (Scheme 112).



Scheme 112 Proposed forward synthesis of bahamaolide A

*Synthesis of sulfoxides **497** and **499***

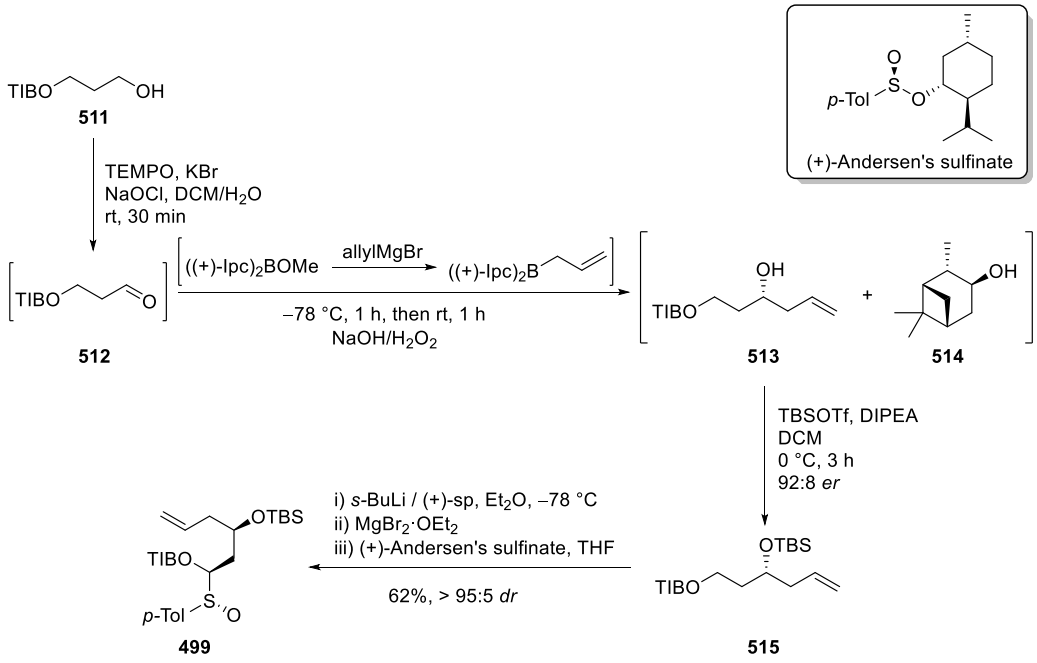
Sulfoxide **497** was synthesised from allylbenzoate (**503**) in four steps (Scheme 113). Hydroboration of **503** using pinacol borane and Wilkinson's catalyst afforded boronic ester **504**, which was sequentially homologated with carbenoids derived from stannane **505** and benzoate **507**. The resulting secondary boronic ester **508** was then stereospecifically oxidised to yield alcohol **509** as a single diastereoisomer as determined by ^{1}H NMR. No intermittent isolation or purifications were performed, thus providing **509** in one pot from boronic ester **504**. TES protection of **509** proceeded in high yield to furnish silyl ether **510**, which was converted to sulfoxide **497** through asymmetric lithiation and trapping with Andersen's chiral sulfinate. The whole process could be performed on gram scale to afford multigram quantities of sulfoxide **497** as a single diastereomer.



Scheme 113 Synthesis of sulfoxide **497**

The synthesis of sulfoxide **499** (Scheme 114) was initiated from alcohol **511**, which was oxidised to aldehyde **512** and subjected to Brown's asymmetric allylation reaction using ((+)-Ipc)$_2$Ballyl to generate homoallylic alcohol **513** as an inseparable mixture with (+)-isopinocampheol (**514**), an expected by-product of the reaction. Protection of both **513** and **514** with TBSOTf proceeded without incident to afford protected alcohol **515**,

which was separated from TBS-protected isopinocampheol by flash column chromatography. The enantiomeric ratio of the reaction was found to be 92:8 by chiral HPLC analysis. The reason for this low value is that the magnesium salts generated when forming ((+)-Ipc)$_2$Ballyl from ((+)-Ipc)$_2$BOMe and vinylMgBr reduce the rate of the allylboration reaction and prevent it entirely at temperatures below –78 °C.[134] In the absence of magnesium salts, allylboration reactions occur instantaneously at –100 °C to give products with >99% *ee*; however, their removal, especially on a large scale, is operationally challenging. Fortunately, the disappointing enantiomeric ratio of **515** was inconsequential as upon forming sulfoxide **499** the minor enantiomer of **515** was transferred to a different diastereomeric series and removed by flash column chromatography, thus yielding sulfoxide **499** in 62% yield and as a single diastereomer.

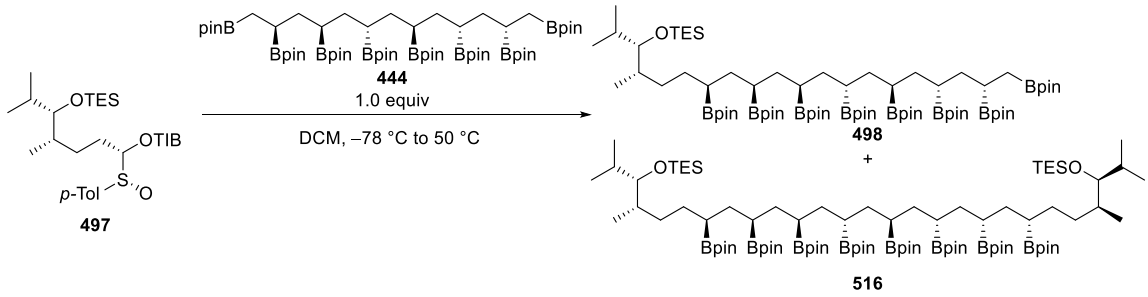


Scheme 114 Synthesis of sulfoxide **499**

*Desymmetrisation of octaboronic ester **444** using sulfoxide **497***

The desymmetrisation of octaboronic ester **444** was next performed using sulfoxide **497**. Replicating the number of equivalents used when desymmetrising **444** with homoallylic sulfoxide **305**—2.5 equiv of **305**, 2.6 equiv of *i*-PrMgCl·LiCl—fully consumed **444** and furnished 37% yield of the desymmetrised product **498** and 48% yield of over homologated octaboronic ester **516** (Table 8, entry 1). This product distribution suggested that a superfluous amount of sulfoxide **497** was being used, so the equivalents of **497** and *i*-PrMgCl·LiCl were reduced to 2.0 and 2.1, respectively (Table 8, entry 2). Under these conditions, the expected statistical distribution of products was restored—51% yield of

desymmetrised product **498**, 27% yield of over homologated product **516** and 24% recovered octaboronic ester **444**—and so these conditions were chosen as optimal. Because all the NMR signals of compound **498** appear in the aliphatic region, it was not possible to determine the *dr* of the iterative diboration–homologation sequence at this point and so the material was moved forward in the sequence with the view to determine the *dr* at a later stage.

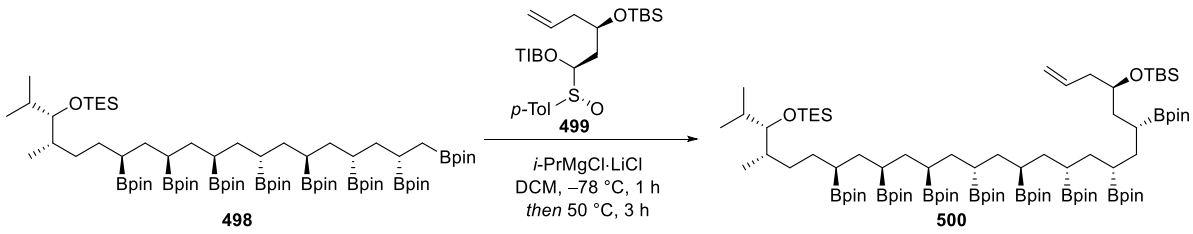


Entry	**497** / equiv	*i*-PrMgCl·LiCl / equiv	Yield **498** / %	Yield **516** / %	Recovered **444** / %
1	2.5	2.6	37	48	0
2	2.0	2.1	51	27	24

Table 8 Desymmetrisation of octaboronic ester **444** with sulfoxide **497**

*Homologation of poly(boronic ester) **498** with sulfoxide **499***

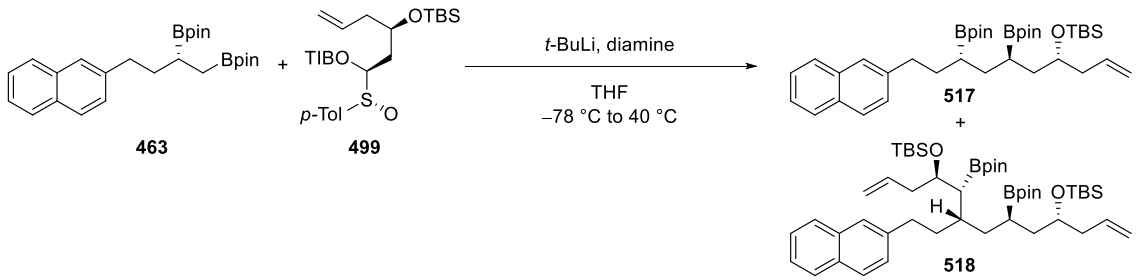
With desymmetrised octaboronic ester **498** in hand, the homologation with sulfoxide **499** was investigated. Treatment of a mixture of 1.0 equiv of octaboronic ester **498** and 1.3 equiv of sulfoxide **499** with 1.4 equiv of *i*-PrMgCl·LiCl in DCM at –78 ˚C for 1 h, followed by heating at 50 ˚C for 3 h resulted in 45% yield of the desired homoallyl containing octaboronic ester **500**. Although low yielding, the reaction was remarkably clean, and the yield could be adjusted to 93% when unreacted starting material was accounted for (Table 9, entry 1). In order to improve consumption of poly(boronic ester) **498** , the reaction was repeated using 2.5 equiv of sulfoxide **499** and 2.6 equiv of *i*-PrMgCl·LiCl, which afforded 56% of **500**; however, consumption of **498** was still poor and the yield could be adjusted to 95% brsm (Table 9, entry 2).



Entry	**498** / mg	**499** / equiv	*i*-PrMgCl·LiCl / equiv	**500** / %
1	20	1.3	1.4	45 (93 brsm)
2	50	2.5	2.6	56 (95 brsm)

Table 9 Homologation of poly(boronic ester) **498** with sulfoxide **499**

Lithiation–borylation reactions using poly(boronic ester) containing fragments such as **498** were hitherto unknown, and so it was not obvious whether fragment **498** or **499** (or both) was responsible for the lack of reactivity. To test whether the carbenoid derived from sulfoxide **499** was a competent reaction partner in lithiation–borylation reactions, **499** was reacted with simple bis(boronic ester) **463** (Table 10). Treatment of a mixture of **463** and sulfoxide **499** with *t*-BuLi at –78 ˚C in THF resulted in 17% yield of the expected product (**517**) and 65% recovered **463** with no over homologation (Table 10, entry 1). This outcome was remarkable because diamine–free lithium carbenoids are known to react with 1,2-bis(boronic esters) non-selectively at both boron centres;[83] whereas, in this case even attack at the primary boron centre is inefficient, which is evidenced by the poor yield and recovery of 65% of **463**. Increasing the equivalents of sulfoxide **499** and *t*-BuLi (1.5 equiv of each) resulted in complete consumption of bis(boronic ester) **463** and led to a modest increase in the yield of 1,3-bis(boronic ester) **517**, but also permitted the formation of over homologation product **518** in 17% yield (Table 10, entry 2). The mass balance of this reaction was poor (47%), which could be due to direct attack of *t*-BuLi to a boronic ester, which would irreversibly form an unproductive boronate complex and thus sequester **463**. Further increasing the equivalents of **499** to 2.0 or 2.5 provided a small increase in the yield of **517** (32% and 36%, respectively); however, the yield of over homologation product **518** also increased (31% and 45% yield, respectively) (Table 10, entries 3 and 4). Remarkably, even with 2.5 equiv of diamine–free carbenoid complete conversion of **463** to **518** was not observed, thus highlighting the poor reactivity of the carbenoid derived from sulfoxide **499**. Incorporation of either PMDTA or TMEDA completely arrested reactivity and permitted the re-isolation of most of the starting material (Table 10, entries 5 and 6).



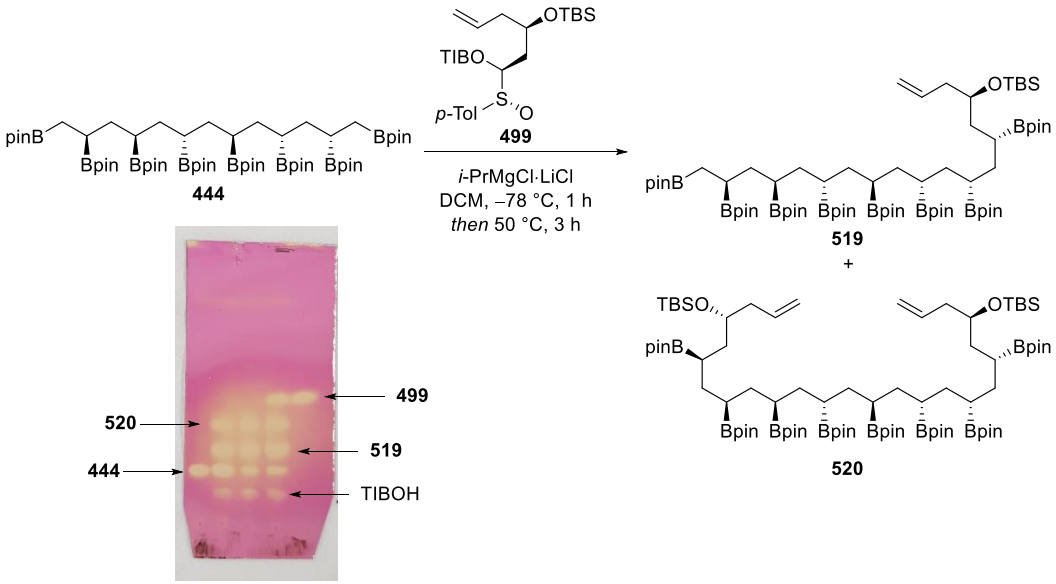
Entry	Sulfoxide / equiv	*t*-BuLi / equiv	Diamine / equiv	**517** / %	**518** / %	**463** / %
1	1.05	1.05	–	17	–	65
2	1.50	1.50	–	30	17	–
3	2.00	2.00	–	32	31	–
4	2.50	2.50	–	36	45	–
5	2.00	2.00	PMDTA 2.00	–	–	80
6	2.00	2.00	TMEDA 2.00	–	–	91

Table 10 Homologation of bis(boronic ester) **463** with sulfoxide **499**

*Desymmetrisation of octaboronic ester **444** using sulfoxide **499***

To overcome the poor reactivity of the carbenoid derived from sulfoxide **499**, it was decided to perform the desymmetrisation of octaboronic ester **444** with homoallylic sulfoxide **499**, and then perform the second challenging homologation with sulfoxide **497**. Desymmetrisation of octaboronic ester **444** with 2.0 equiv of sulfoxide **499** proceeded to furnish 36% of desired product **519** and 18% of the over homologated octaboronic ester **520** with 45% of octaboronic ester **444** remaining (Table 11, entry 1). Increasing the number of equivalents of sulfoxide **499** to 2.5 restored the statistical product distribution and allowed desymmetrised octaboronic ester **519** to be isolated in 47% yield (Table 11, entry 2). As in the case of previous desymmetrisation reactions the purification of **519** was challenging as **520** and **444** were difficult to separate. In addition to this, **519** showed some instability to silica gel chromatography, as determined by 2D TLC analysis, which dictated that any chromatographic purification be performed rapidly. Fortunately, fast purification using an automated Biotage Isolera one system with a hexane/acetone gradient permitted the complete separation of **519** from **520** and **444**. Unfortunately, the reaction proved to not be readily scalable, and increasing the scale of the reaction to 330 mg of octaboronic ester **444** resulted in a substantial drop in yield (Table 11, entry 3). This decrease in yield was found to be due to the instability of the product during

purification. The expected yield was restored by splitting the crude reaction mixture into multiple 50 mg sized batches that were chromatographed separately.



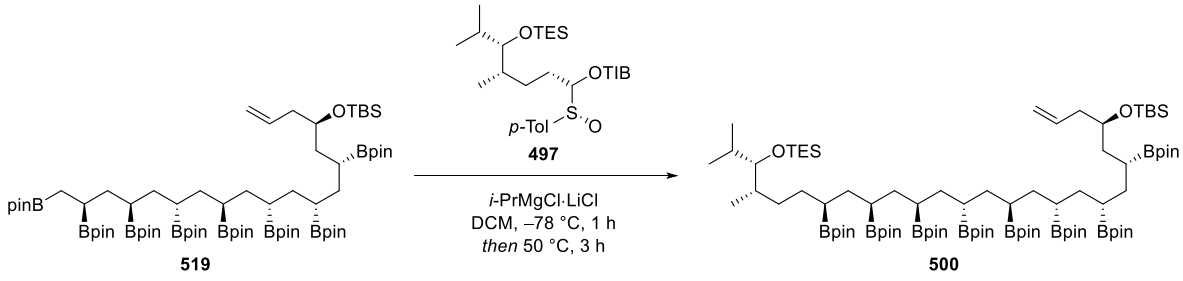
Entry	Scale / mg	**499** / equiv	*i*-PrMgCl·LiCl / equiv	Yield **519** / %	Yield **520** / %	Recovered **444** / %
1	50	2.0	2.1	36	18	45
2	50	2.5	2.6	47	23	26
3	330	2.5	2.6	32	not recorded	not recorded

Table 11 Desymmetrisation of octaboronic ester **444** with sulfoxide **499**

*Homologation of poly(boronic ester) **498** with sulfoxide **497***

The homologation of desymmetrised octaboronic ester **519** with sulfoxide **497** proved to also be challenging but was ultimately solved using a brute force approach. Homologation of **519** with 2.0 equiv of sulfoxide **497** gave a very clean reaction, where the crude reaction mixture consisted only of product, starting material and the expected by-products of the reaction; however, the yield of the reaction was only 54% and consumption of the starting material was low (Table 12, entry 1). Drastically increasing the equiv of **497** and *i*-PrMgCl·LiCl to 4.0 and 4.1, respectively, resulted in a similarly clean reaction and a higher yield (65%); however, full consumption of the starting material was still not achieved (Table 12, entry 2). Finally, complete conversion of the starting material was achieved when using 5.0 equiv of **497** and 5.1 equiv of *i*-PrMgCl·LiCl, which afforded poly(boronic ester) **500** in 72% yield (Table 12, entry 3). The low reactivity of the carbenoid derived from sulfoxide **497** with poly(boronic ester) **519** was disappointing because **497** is a precious reagent that takes five steps to synthesise and using it in

5.0 equiv excess would require access to multi-gram quantities. Fortunately, this requirement proved to be feasible because the assembly–line methodology[52] used to construct **497** could be performed efficiently using 5 g of boronic ester **504** with no loss in yield or selectivity.



Entry	**497** / equiv	*i*-PrMgCl·LiCl / equiv	Yield **500** / %
1	2.0	2.1	54 (86 brsm)
2	4.0	4.1	65 (83 brsm)
3	5.0	5.1	72

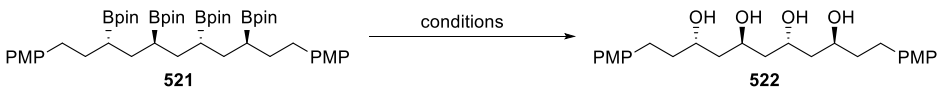
Table 12 Homologation of poly(boronic ester) **519** with sulfoxide **497**

*Oxidation of poly(boronic ester) **500***

The oxidation of tetra(boronic ester) **521** has been shown in our group by Dr Hsuan-Hung Liao, who found that whilst basic hydrogen peroxide afforded polyol **522** in 73% yield, the urea·H_2O_2 complex was a superior oxidant for this transformation and generated **522** in 93% yield (Scheme 115a). Due to this precedent the oxidation of poly(boronic ester) **500** was investigated using urea·H_2O_2. In a first reaction, poly(boronic ester) **500** was treated with 60 equiv of urea·H_2O_2 at 50 °C for 16 h. Remarkably, LCMS analysis suggested complete conversion to poly(alcohol) **523**, where all eight boronic esters had been oxidised and the TES silyl ether had been removed. Cleavage of the TES group is a fortuitous result as its selective removal was originally planned as a discreet step. Other oxidants were also tested in this process—NaOH/H_2O_2, $NaBO_3$—but did not deliver complete conversion of **500** to **523** as judged by LCMS analysis. Cognisant of the propensity of hydrogen peroxide to form explosive adducts with acetone, dimethyl sulfide (2.0 equiv w.r.t urea·H_2O_2) was added after the oxidation step to reduce the excess H_2O_2 before the addition of dimethoxy propane and CSA. Initially, dimethoxy propane and CSA were added directly to the reaction mixture after removal of the volatile components, but conversion of **523** to **494** was slow and could not be pushed to completion. It was found that removal of urea following oxidation was beneficial to the reaction, which went

to completion after a filtration through celite; however, the yield was low. Changing the filter pad from celite to sand had a positive influence on the yield—presumably because the celite was retaining some of the polyol components of the reaction. Poly(acetonide) **494** was then afforded in 58% yield over 2 steps from **500** and with >95:5 *dr*. Although 58% is a good yield for a transformation of this complexity, this step should still be considered a bottleneck as the theoretical yield of the transformation is half of the mass of the starting material (**500**) that was engaged in the reaction. This feature greatly increased the difficulty associated with accessing sufficient amounts of compound **494** to complete the synthesis. Because the steps to convert octaboronic ester **444** to poly(acetonide) **494** are known to be stereospecific—homologation of a boronic ester with an enantiopure carbenoid, oxidation and acetonide protection—the *dr* of octaboronic ester **444** was assumed to have also been >95:5.

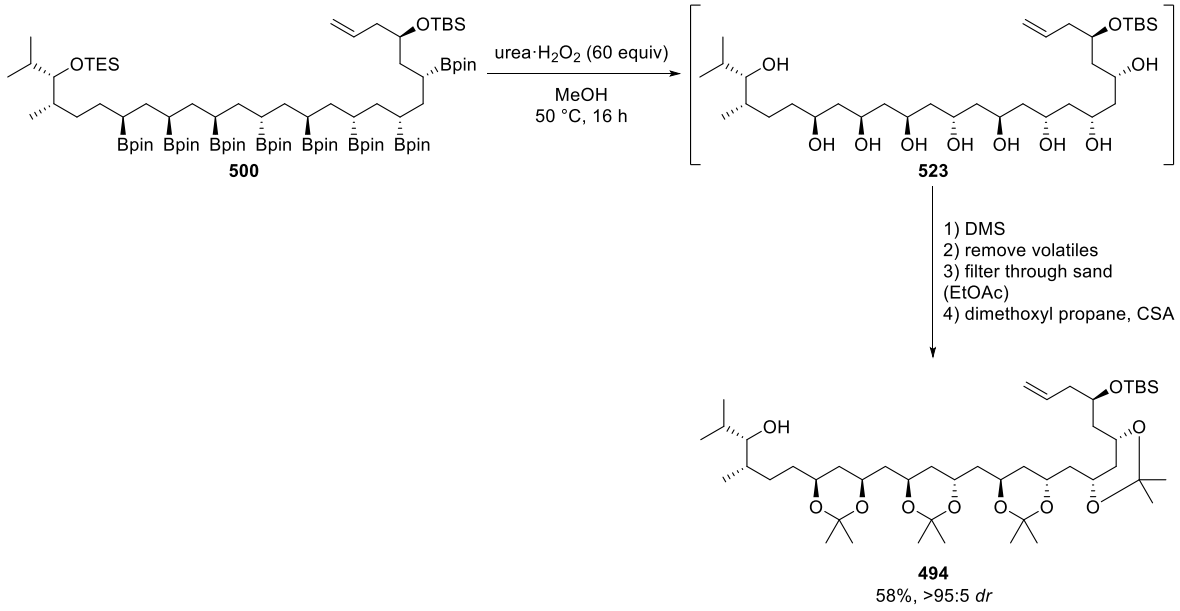
a)



521 **522**

Entry	Conditions	Yield / %
1	NaOH, H_2O_2, THF, rt, 16 h	73
2	Urea·H_2O_2, MeOH, 50 °C, 16 h	93

b)



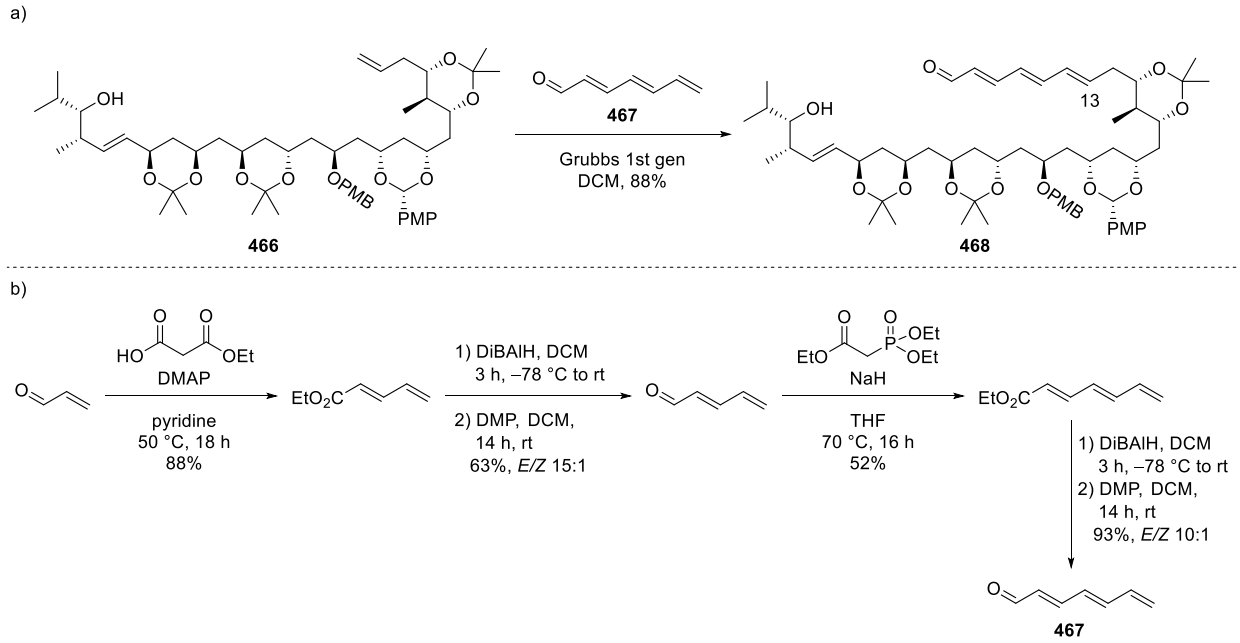
500 **523** **494**

58%, >95:5 *dr*

Scheme 115 Oxidation of poly(boronic ester) **500**

Synthesis of the polyene portion

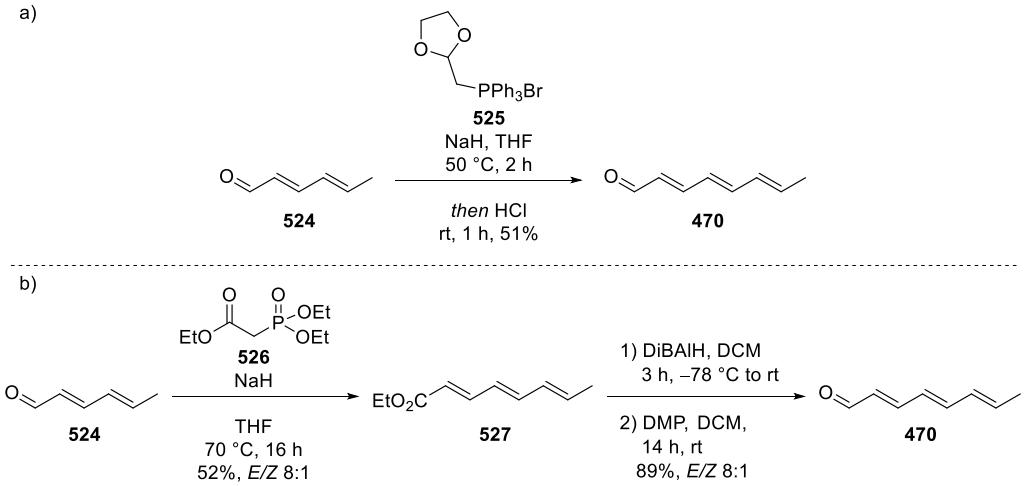
With the polyol portion of bahamaolide A successfully constructed, we turned our attention to the installation of the polyene and formation of the macrocycle. Sammakia has shown that cross metathesis between aldehyde **467** and compound **466** proceeded with 88% yield and an *E/Z* ratio of 5:1 favouring the desired diastereomer at the C-13 double bond when using Grubbs first generation catalyst (Scheme 116a).[125] According to Grubbs' terminology, this represents a selective cross-metathesis reaction between a type 2 (**467**) and a type 3 (**466**) olefin.[135] A disadvantage of this process was that the synthesis of aldehyde **467** was cumbersome and required six steps, four of which were oxidation level changes (Scheme 116b).[124]



Scheme 116 Sammakia's cross-metathesis of trienal **467** with compound **466** and synthesis of trienal **467**

We envisioned that this process could be improved by utilising trienal **470**, which can be obtained in one step from commercially available sorbaldehyde (**524**). The terminal alkene of trienal **470** should also be a type 2 olefin and should engage in a selective cross-metathesis reaction with compound **494**. Moreover, the presence of the terminal methyl group should increase the electron density of the terminal olefin with respect to **467**, thus promoting the desired transformation. Synthesis of **470** was first investigated using a Wittig reaction between sorbaldehyde (**524**) and phosphonium salt **525**, which generated trienal **470** in 51% yield (Scheme 117a). Although **470** appeared to be one spot by TLC analysis, the ^{1}H NMR spectrum suggested that there were at least four compounds present, the relative ratios of which could not be determined due to overlap of the

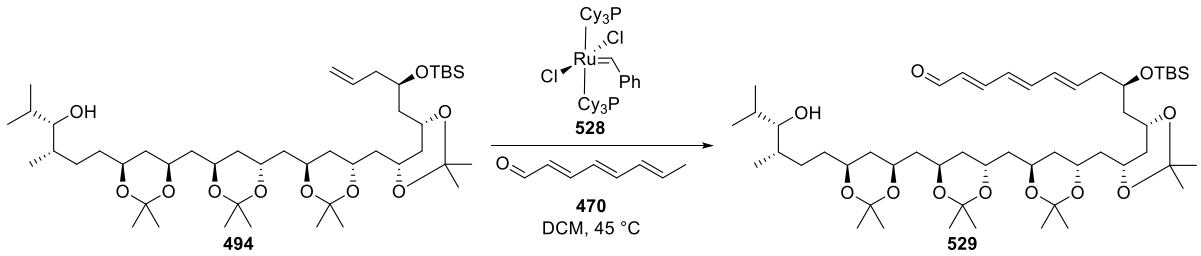
resonances. Unfortunately, the *E/Z* ratio could not be improved through chromatography using SiO_2 or $AgNO_3$-doped SiO_2 as the stationary phase, or by distillation. Due to time pressure the metathesis reaction and subsequent steps were performed using **470** derived from the reaction shown in Scheme 117a; however, we later found that **470** was generated with an improved *E/*Z ratio of 8:1 when using a HWE reaction to forge the β-alkene (Scheme 117b). Specifically, deprotonation of **526** with NaH and addition of **524** generated conjugated ester **527** in 52% yield and with an *E/Z* ratio of 8:1. Conversion of **527** to trienal **470** through a two-step reduction–oxidation sequence proceeded in high yield with no loss of *E/Z* selectivity.



Scheme 117 Synthesis of trienal **470**

Trienal **470** was then engaged in a metathesis reaction with poly(acetonide) **494**. In the first instance, the reaction was performed with 4.2 equiv of **470** and 5.0 mol% of Grubbs first generation catalyst (**528**) in DCM at reflux. After 6 h, TLC analysis showed the presence of both starting materials, **494** and **470**, as well as a single new spot whose MW matched that of **529** as judged by TLC-MS analysis. The absence of homodimers of **470** and **494** suggested that their classification as type 2 and type 3 olefins, respectively, was correct. At this point a further 5.0 mol% of **528** was added and the reaction was stirred for a further 16 h, at which point TLC analysis showed that **494** had still not been fully consumed, but no other species were apparent. The reaction was then stopped, and aldehyde **529** was obtained in 65% yield (91% brsm) after purification by flash column chromatography (Table 13, entry 1). Although **529** was one spot by TLC analysis, ^{1}H and ^{13}C NMR analysis showed **529** to be a mixture of double bond isomers; however, the diastereomeric ratio could not be determined due to overlapping resonances. The yield of the reaction could be improved to 73% (89% brsm) by increasing the equivalents of **470**

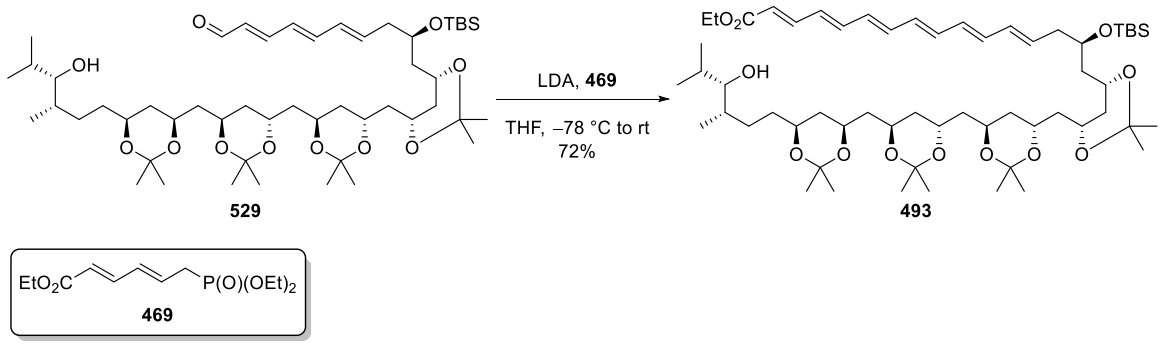
and **528** to 10 and 20 mol%, respectively (Table 13, entry 2), although the reactio149n still did not go to completion.



Entry	**470** equiv	**528** equiv	Yield / %	Yield brsm / %
1	4.2	0 h: 5.0 mol% 6 h: 5.0 mol% Total: 10 mol%	65	91
2	10	0 h: 10 mol% 6 h: 10 mol% Total: 20 mol%	73	89

Table 13 Cross-metathesis of poly(acetonide) **494** with trienal **470**

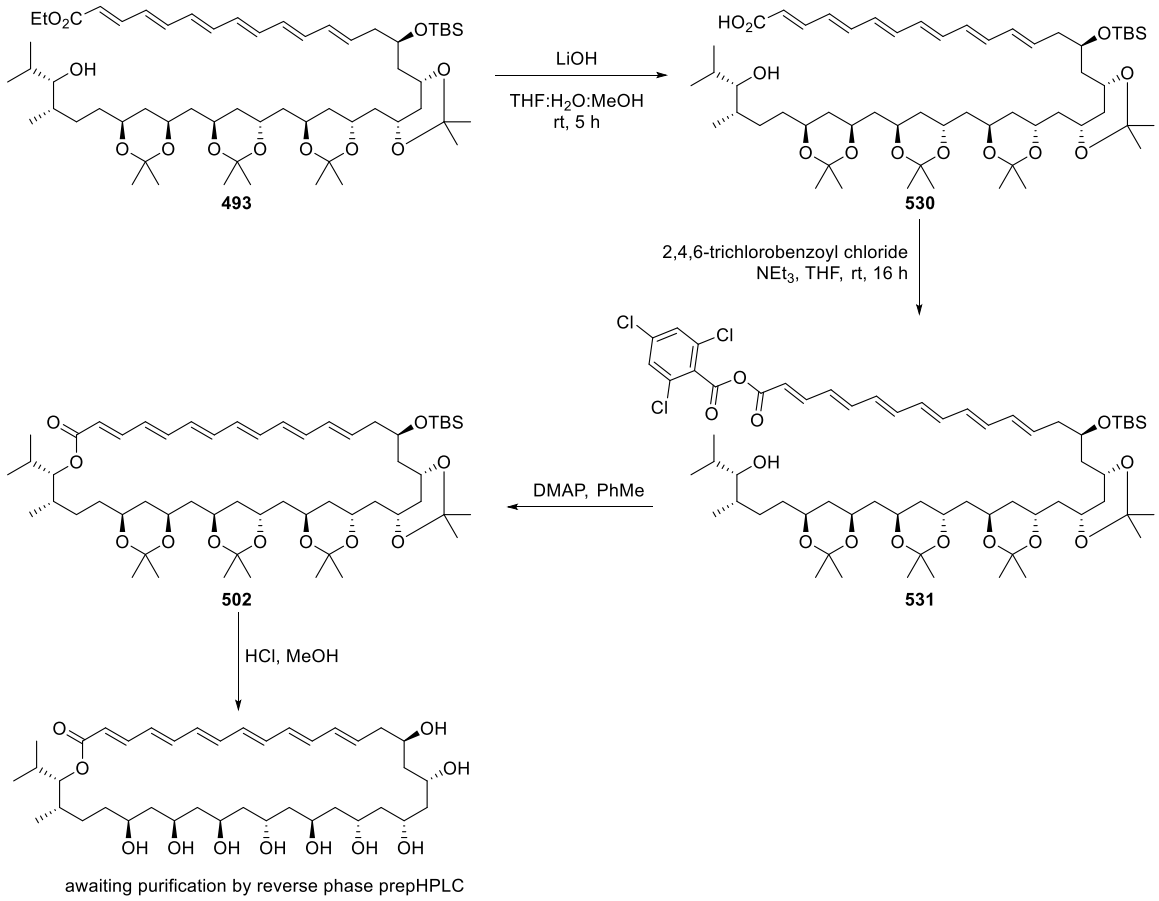
The HWE reaction with known phosphonate **469**[136] proceeded without incident to furnish hexaene **493** in 72% yield (Scheme 118).



Scheme 118 Horner-Wadsworth-Emmons reaction with aldehyde **529** and phosphonate **469**

The final steps were performed without isolation of any intermediates (Scheme 119). Saponification of ester **493** with LiOH proceeded to deliver carboxylic acid **530**, which was subjected to Yamaguchi's macrolactonisation conditions without purification. Carboxylic acid **530** was treated with 2,4,6-trichlorobenzoyl chloride and Et_3N to generate mixed anhydride **531**. Evans showed in his synthesis of (+)-roxaticin that decomposition occurred if the mixed anhydride was not isolated before being added to a solution of DMAP in PhMe.[107] In light of this precedent, **531** was filtered through a pad of celite before being concentrated and re-dissolved in anhydrous PhMe (0.002 M). The solution of **531** was then added to a solution of DMAP in PhMe (0.009 M) over 6 h, which generated protected bahamaolide A (**502**). Sammakia has shown that the corresponding

intermediate in the synthesis of dermostatin A was unstable to purification[125] and so **502** was only purified using a rudimentary filtration through a small pad of silica gel and was characterised only by HRMS. Deprotection of poly(acetonides) to yield oxopolyene macrolides is notoriously difficult in the literature. In the most extreme example, Evans opted to use the more labile cyclopentyl ketals in his synthesis of (+)-roxaticin due to the challenges associated with acetonide removal.[107] Despite this, the use of DOWEX resin in MeOH[100,111,113] or HCl in MeOH[124,125] have emerged as standard methods to achieve this transformation. We opted to use HCl in MeOH as Sammakia showed these conditions were successful in the deprotection of the structurally related dermostatin A.[125] Protected bahamaolide A (**502**) was treated with HCl in MeOH at room temperature for 16 h, after which LCMS analysis suggested the formation of 3 peaks with the correct mass for bahamaolide A, which presumably corresponded to the desired product and double bond isomers. Unfortunately, the reaction was not complete, as other species corresponding to partial deprotection were also detected. Resubjecting the crude mixture to the reaction conditions for a further 16 h afforded complete conversion of the peaks corresponding to incomplete deprotection to peaks with the correct mass for bahamaolide A. Regretfully, at the time of writing the purification of bahamaolide A had not yet been performed due to technical difficulties regarding our group's reverse phase prepHPLC machines. A crude sample of bahamaolide A has been synthesised and is awaiting purification.



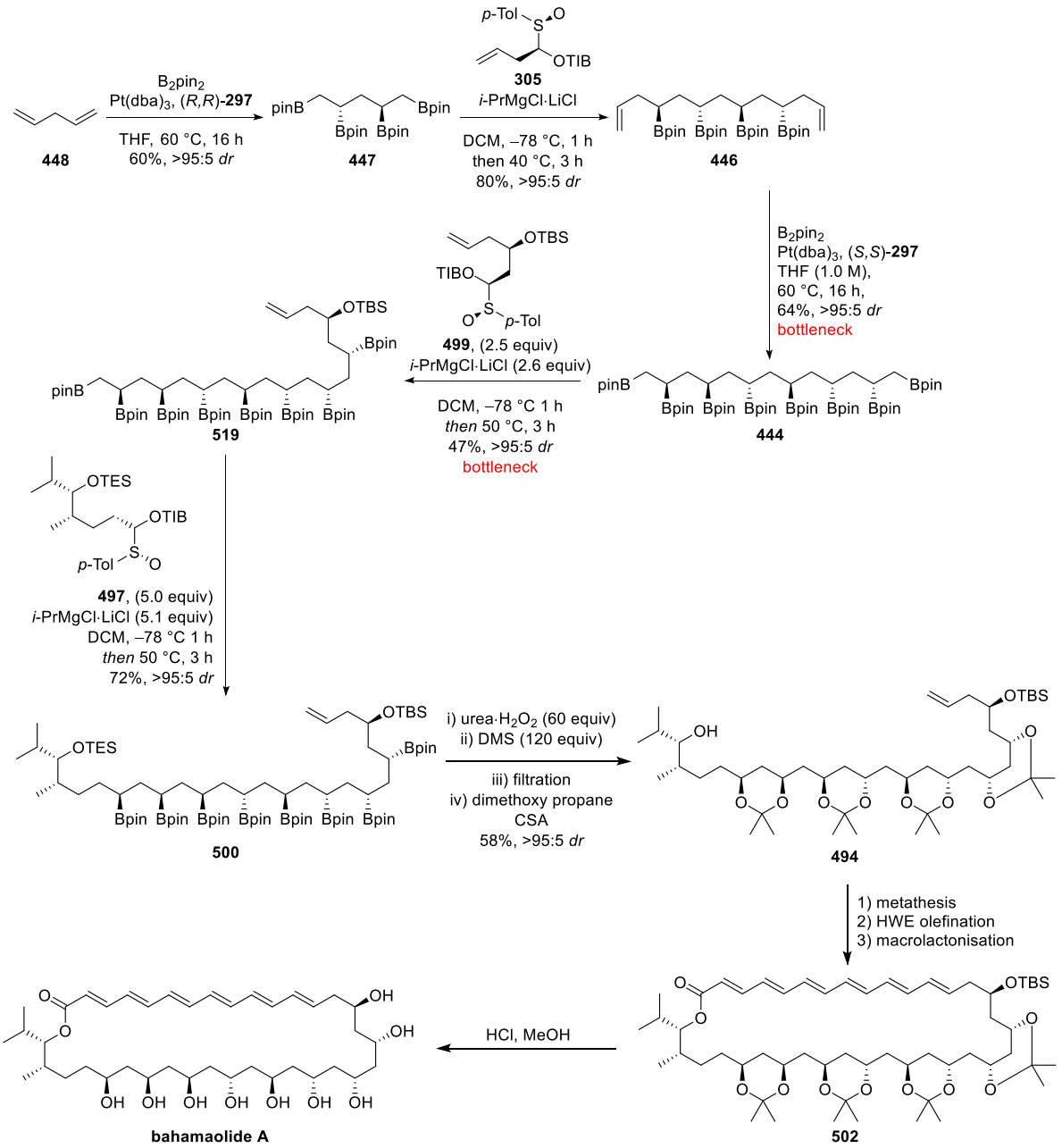
493 530 531 502

Scheme 119 Synthesis of a crude sample of bahamaolide A

Conclusion

The synthesis of the polyol portion of bahamaolide A using an iterative, bi-directional homologation–diboration–homologation sequence has been successfully realised (Scheme 120). Using this protocol, 8 stereogenic centres were set with complete enantio- and diastereocontrol in just 5 steps, thus displaying the power of this methodology. However, of the 7 steps to transform 1,4-pentadiene into poly(acetonide) **494**, 2 were bottleneck steps; specifically, 1) the double diboration of tetraboronic ester **446** to afford octaboronic ester **444**, which required a very challenging column that took 6–8 h to complete and was limited by scale, and 2) the desymmetrisation of octaboronic ester **444** with sulfoxide **499**, which also required a very challenging column that was limited by scale and was further complicated by the instability of **519** to silica gel. In addition to this, carbenoid precursors **499** and **497** were used in 2.5 and 5.0 equivalents excess, respectively. The reality of this was that while the reactions themselves were robust, the main challenge of the project was purification and accessing enough material to push

forward to the later steps. Nevertheless, enough poly(acetonide) **494** was obtained to test the literature known steps to construct the polyene and close the macrocycle. The metathesis reaction between poly(acetonide) **494** and trienal **470** successfully gave the product, but before this project will be ready for publication this step will have to be repeated using a trienal with a higher *E/Z* ratio, be that trienal **470** made according to Scheme 117b or trienal **467** as used by Sammakia.[124,125] The subsequent steps were also shown to work as documented in the literature, which allowed the formation of presumed protected bahamaolide A (**502**) without incident or upset. LCMS proved to be an invaluable tool to analyse the deprotection of **502** to bahamaolide A, and we currently have a crude sample of the natural product awaiting purification by reverse phase prepHPLC.

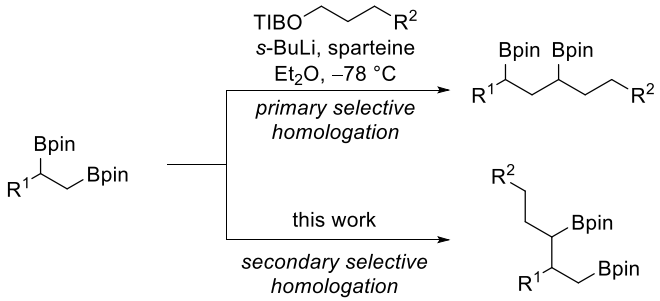


Scheme 120 Synthesis of bahamaolide A

Chapter 3: Towards a Novel Boronic Ester Protecting Group

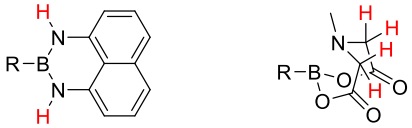
Project proposal

Having developed an efficient process for the homologation of 1,2-bis(boronic esters) through the less hindered terminal boron centre using sparteine coordinated lithiated benzoates and carbamates,[83] we were interested to see whether we could develop a complementary procedure to selectively homologate 1,2-bis(boronic esters) through the more hindered internal boronic ester (Scheme 121).



Scheme 121 Proposed homologation of 1,2-bis(boronic esters) through the more hindered secondary boronic ester moiety

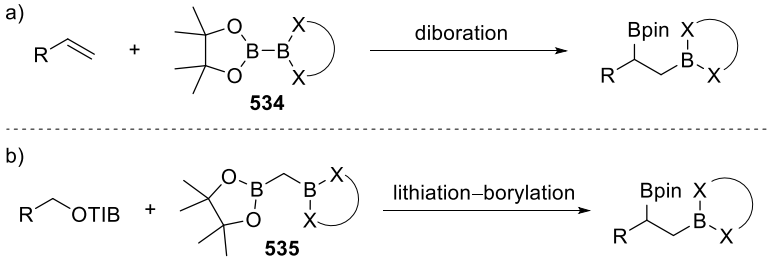
We rationalised that selectivity for the secondary boronic ester of a 1,2-bis(boronic ester) in a lithiation–borylation reaction could be achieved by protecting the primary boronic ester with a ligand that lowers its Lewis acidity relative to a pinacol boronic ester by filling, or partially filling its vacant p-orbital. On inspection of successful methods from the literature, boron protection includes forming a diazaboronic ester, such as in Suginome's diaminonaphthaline (DAN) ligand (**532**),[137] or by having a tethered moiety with a lone pair available for direct donation into the empty p-orbital of the boron atom, such as in Burke's *N*-methyliminodiacetic acid (MIDA) boronate (**533**) (Figure 5).[138] Due to the presence of acidic protons, both the DAN (**532**) and MIDA (**533**) groups are incompatible with lithiation−borylation reactions, as they would quench the lithiated carbenoids and prevent formation of boronate complexes. In addition to this, the MIDA boronate also contains unprotected carbonyl groups that would be subject to attack from organolithiums. We therefore aimed to develop a novel boron protecting group that is compatible with lithiation−borylation methodology.



532 533

Figure 5 Suginome's DAN and Burke's MIDA ligands for boronic acids

Once such a group has been identified the synthesis of primary protected 1,2-bis(boronic esters) will be investigated using diboron reagents **534** and **535**. It was envisioned that that desired compounds could be accessed through diboration of a terminal alkene with **534** (Scheme 122a), or through a lithiation-borylation reaction between diboron compound **535** and a primary benzoate (Scheme 122b).

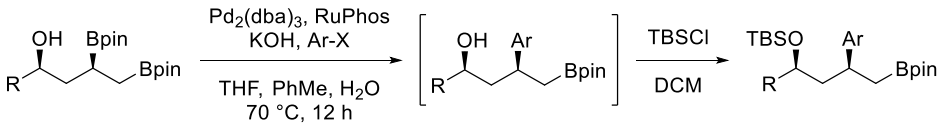


Scheme 122 Proposed synthesis of differentially protected 1,2-bis(boronic esters) using diboron reagents **534** and **535**

Introduction

Selective functionalisation of a 1,2-bis(boronic ester) through the secondary boron moiety

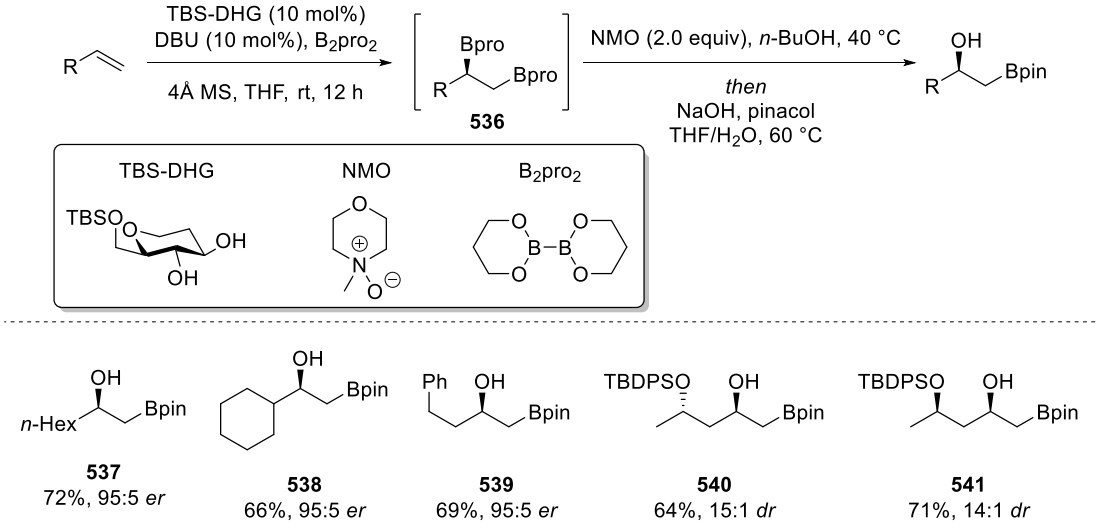
Morken has shown that 1,2-bis(boronic esters) which contain a proximal hydroxyl group undergo Suzuki coupling reactions through the more hindered secondary boronic ester moiety with retention of stereochemistry (Scheme 123).[139] The origin of the regiochemical outcome of the reaction was a substrate directed transmetallation event, whereby the hydroxyl group formed a covalent link with the palladium and thus directed it to the internal boronic ester.



Scheme 123 Morken's hydroxyl directed coupling reaction

Morken has also shown that a tandem diboration/mono-oxidation can be achieved in a one-pot process starting from a terminal alkene (Scheme 124).[140] Asymmetric carbohydrate catalysed diboration[141,142] using B_2pro_2 as the diboron source afforded 1,2-bis(boronic ester) **536**, which was immediately subjected to an oxidation reaction

with *N*-methyl morpholine-*N*-oxide. The regiochemical preference of the oxidation step for the internal boronic ester is due to the 1,2-migration being the rate limiting step when using NMO as the oxidant. Because the formation of a boronate complex is reversible and the 1,2-migration is slow, the more substituted and electron rich secondary carbon atom undergoes metallate rearrangement preferentially. Transesterification of the remaining boronic ester with pinacol generated an isolable species. The scope of the transformation was broad and tolerated mono- and 1,1-disubstituted alkenes to give the corresponding products **537**, **538** and **539** in high yield and with excellent *er*. The diboration phase was insensitive to nearby stereogenic centres, as shown by **540** and **541**, which were isolated in similarly high yield and diastereomeric ratio.

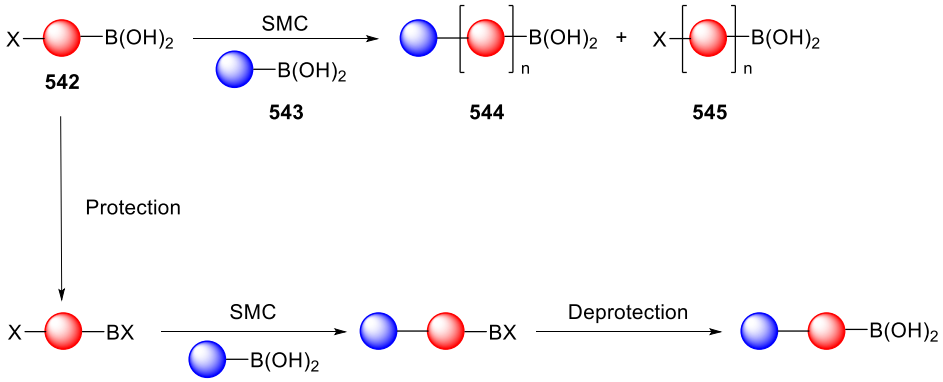


Scheme 124 Morken's secondary selective oxidation of 1,2-bis(boronic esters)

Literature known boronic ester protecting groups

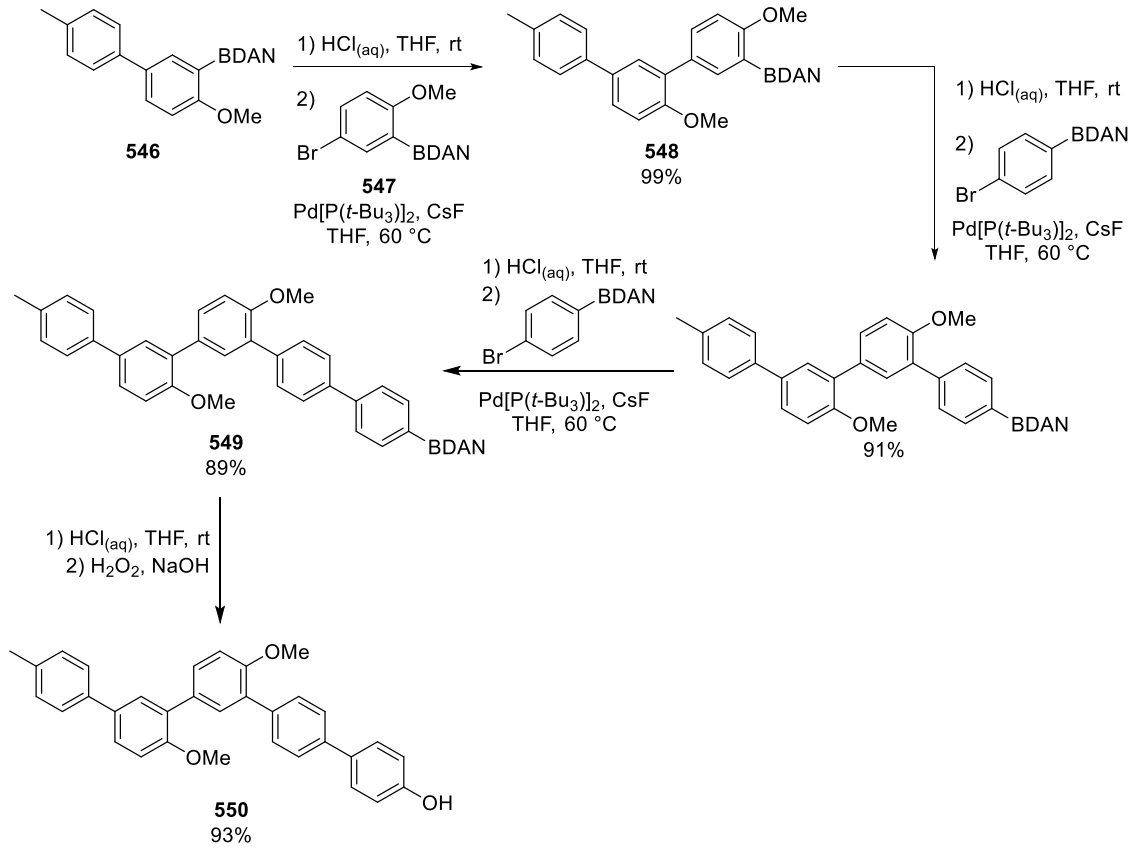
Heteroatoms adjacent to boron possessing lone pairs are capable of π overlap into the vacant p-orbital of boron.[143] Nitrogen is less electronegative than oxygen and so is better at donating electron density through induction, as is the case for the DAN ligand. In contrast to this, the conformation of the MIDA boronate allows the donation of the nitrogen lone pair directly to the empty boron p-orbital. Generally, protecting groups with a tethered donating group will reduce the Lewis acidity of boron to a greater extent than those functioning through an inductive effect, and indeed it is possible for a tethered group to form a full boronate complex. Both the DAN and MIDA groups were designed to be used in iterative Suzuki-Miyaura coupling reactions (Scheme 125). To perform iterative Suzuki-Miyaura reactions, one of the coupling partners must contain both an electrophilic component—a halogen or pseudo-halogen—and a nucleophilic component—a boronic acid—such as in compound **542**. Without an efficient protecting-group strategy, a

Suzuki-Miyaura reaction between **542** and boronic acid **543** would result in the desired coupling plus an '*n*' amount of bis(functionalised) coupling partner (**544**), and the polymerisation of the bis(functionalised) coupling partner (**545**). To prevent these undesired processes, the bis(functionalised) coupling partner should be protected at boron. After deprotection of the cross-coupled product, another Suzuki-Miyaura coupling could be performed, which would result in an iterative chain extension.



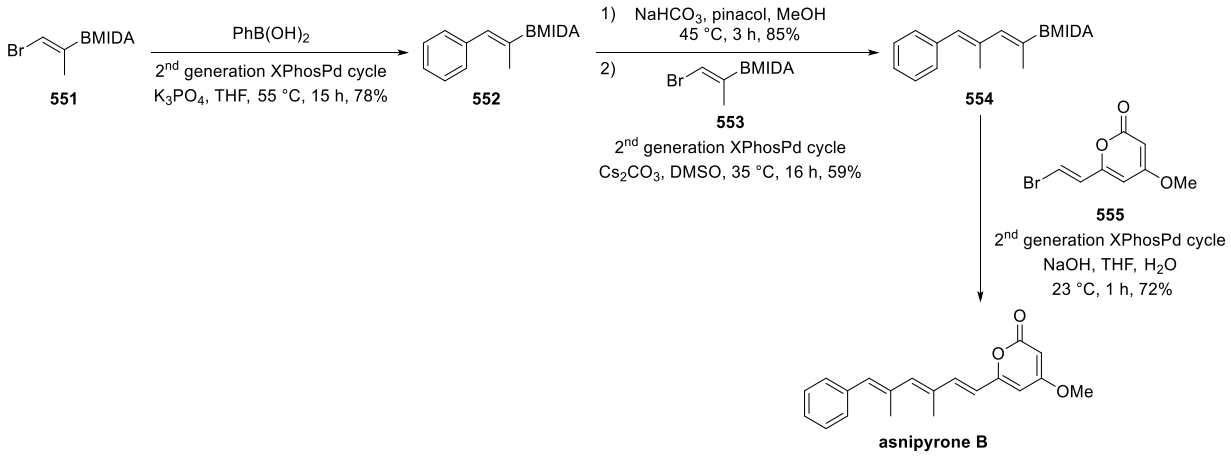
Scheme 125 Method of protection in an iterative SM process

Suginome has applied an iterative Suzuki-Miyaura strategy to the synthesis of oligoarenes using diaminonaphthalene as the boron protecting group.[137,144] In one example the synthesis of phenol **550** was achieved in excellent yield in 8 steps from dan-protected boronic acid **546**. Deprotection of **546** under aqueous acidic conditions furnished the corresponding boronic acid, which was subjected to a palladium-catalysed cross-coupling reaction with aryl bromide **547** to afford DAN-protected boronic ester **548**. A further two iterative cycles of deprotection and cross-coupling generated DAN-protected boronic ester **549**, which was deprotected and the resulting boronic acid oxidised to yield phenol **550** (Scheme 126).



Scheme 126 Suginome's synthesis of oligoarene **550**

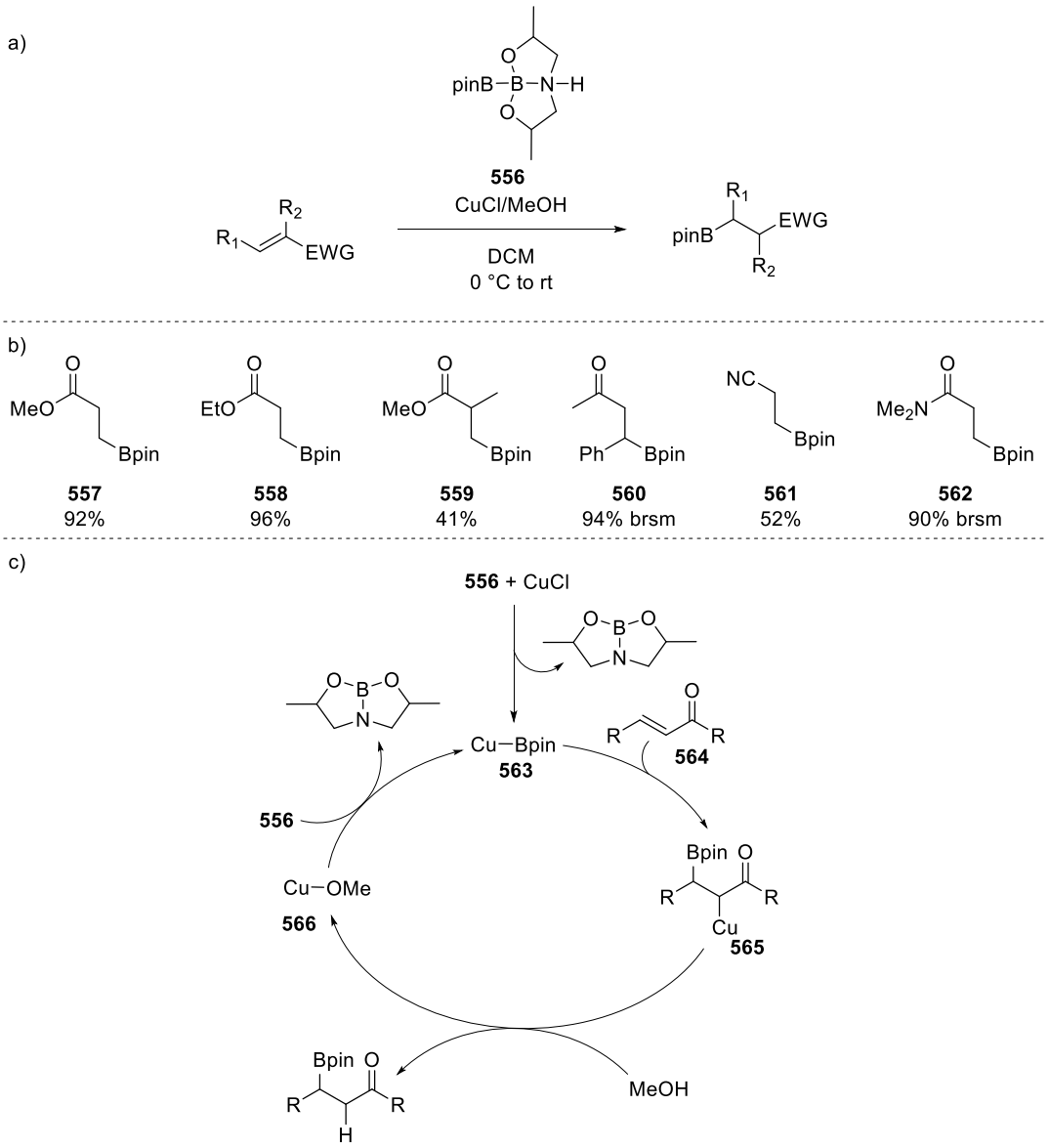
Burke has applied an iterative Suzuki-Miyaura strategy to the synthesis of many polyene containing natural products using *N*-methyliminodiacetic acid as the boron protecting group.[145] Most notably, Burke's iterative procedure could be performed in a fully automated manner, thus allowing for the rapid synthesis of libraries of polyene and polyaryl products.[146] In one example, the synthesis of asnipyrone B was achieved in 4 steps from MIDA-protected boronic ester **551**. Suzuki reaction between **551** and phenylboronic acid generated MIDA-protected boronic ester **552**. Deprotection of the MIDA boronate under basic conditions in the presence of pinacol generated the corresponding pinacol boronic ester, which underwent a Suzuki reaction under anhydrous conditions with vinyl bromide **553**. Anhydrous conditions are required to preserve the MIDA-protecting group of **553**, which would otherwise be deprotected in the basic aqueous media required for the Suzuki-Miyaura cross-coupling reaction. Asnipyrone B was achieved following a further cross-coupling step with vinyl bromide **555** (Scheme 127).



Scheme 127 Burke's synthesis of asnipyrone B

Literature known differentially protected diboron reagents

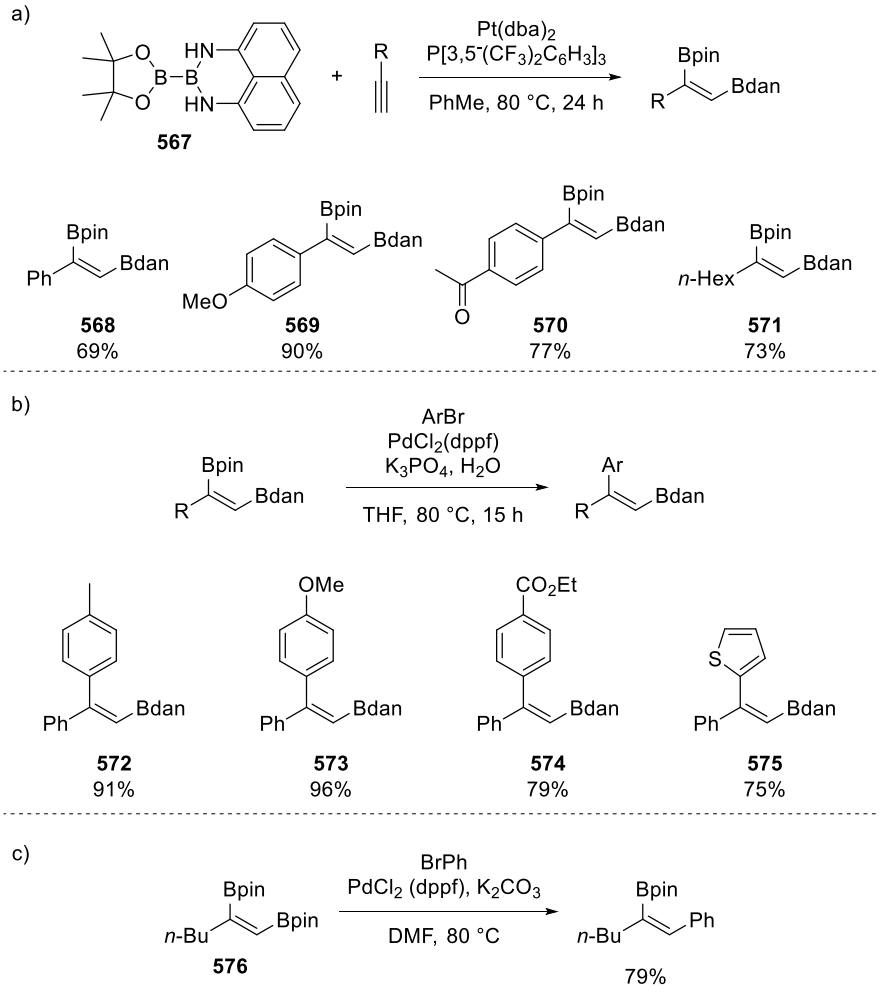
Santos has shown both the synthesis of mixed diboron **556**, which was the first example of a non-symmetrical sp^2–sp^3 hybridised diboron compound, and its utility in the β-borylation of α, β-unsaturated compounds.[147,148] Treatment of **556** and an α, β-unsaturated compound with CuCl and MeOH in DCM resulted in efficient β-borylation (Scheme 128a). The reaction tolerated unsubstituted α, β-unsaturated esters **557** and **558**, as well as substitution at the 3 and 4 positions, as exemplified by examples **559** and **560**, respectively. Other electron withdrawing groups, such as cyano (example **561**) and an amide (example **562**) also performed well under the reaction conditions (Scheme 128b). Because **556** contains an sp^3 hybridized boron moiety, σ-bond metathesis with CuCl occurs spontaneously without prior activation of the boron source with a base or phosphine ligand to afford the active borylating species **563**. This represents an advantage over platinum,[149–151] rhodium,[152] nickel[153] and copper[154] catalysed borylation of α, β-unsaturated esters in that the reaction conditions are milder. Copper species **563** then transfers the Bpin moiety to the 4-position of α, β-unsaturated species **564** to generate **565**, which is subsequently quenched with a proton to yield the product. A σ-bond metathesis reaction between copper species **566** and **556** regenerates **563** and closes the catalytic cycle (Scheme 128c).



Scheme 128 Santos' β-borylation of α,β-unsaturated compounds

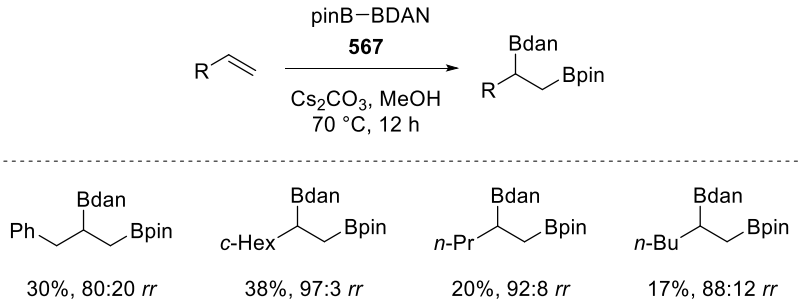
Suginome has shown that diboration of terminal alkynes with the unsymmetrical diboron reagent **567** generates unsaturated, differentially protected 1,2-bis(boronic esters).[155] Significantly, the reaction has a strong regiochemical preference, with the less Lewis acid DAN-protected boron moiety placed at the terminal position (Scheme 129). The reaction tolerated a range of aromatic alkynes, including electron neutral (**568**), electron rich (**569**) and electron deficient (**570**) alkynes. Aliphatic alkynes were also competent reaction partners, as exemplified by example **571**, which was isolated in 73% yield (Scheme 129a). Moreover, the products underwent a subsequent Suzuki-Miyaura coupling reaction selectively at the more hindered internal pinacol boronic ester to yield products **572**–**575** (Scheme 129b). This reactivity is in contrast to the complementary bis(pinacolato)

unsaturated 1,2-bis(boronic ester) **576**, which engaged in a cross-coupling reaction at the less hindered primary boronic ester (Scheme 129c).[156]



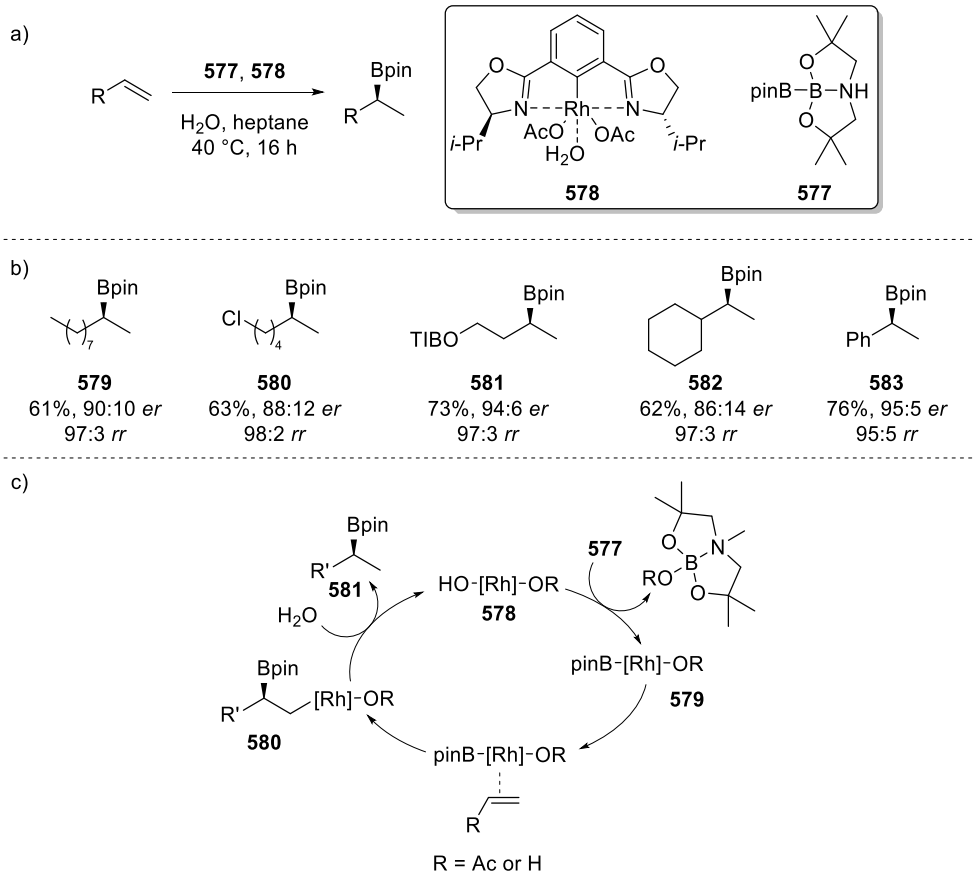
Scheme 129 Regioselective diboration of terminal alkynes with diboron **567** and subsequent cross-coupling reaction

Fernandez has shown that alkenes can undergo metal free diboration reactions with diboron **567** to yield differentially protected 1,2-bis(boronic esters);[157] however, in this case the major regioisomer has the DAN-protected boronic ester at the internal position (Scheme 130). A modest substrate scope of alkyl alkenes was presented, but the regiomeric ratio values varied wildly depending of the substate and the isolated yields obtained were generally poor, which was attributed to partial decomposition of the products upon isolation. Moreover, styrenyl substrates did not furnish the desired diborated products but instead underwent anti-Markovnikov hydroboration of the Bdan moiety.



Scheme 130 Fernandez's metal-free diboration of alkenes with mixed diboron **567**

Aggarwal has shown the asymmetric Markovnikov hydroboration of unactivated terminal alkenes, using mixed diboron **577** and chiral rhodium catalyst **578** (Scheme 131a).[158] The reaction worked well for primary alkenes, yielding the desired products in high yield and with excellent *rr* values; however, the *er* values were comparatively low (**579** and **580**). Interestingly, incorporation of a carbonyl moiety at the position δ to the alkene resulted in increased enantioenrichment, as displayed in compound **581**. Secondary alkenes could also be employed to yield the resulting boronic esters in high yield and *rr* values, but at the detriment of enantiomeric excess (example **582**). Styrenyl alkenes were also excellent reaction partners, with styrene itself yielding **583** in 95:5 *er* (Scheme 131b). The reaction operates under the same mechanistic manifold as Nishiyama's diboration reaction.[159] σ-Bond metathesis between catalyst **578** and diboron **577** generates rhodium-boryl species **579**, which undergoes an enantioselective migratory insertion process with an alkene to generate intermediate **580**. Protodemetallation of **580** with H_2O furnishes hydroboration product **581** and regenerates the active catalyst, thus closing the catalytic cycle (Scheme 131).



Scheme 131 Aggarwal's Markovnikov hydroboration of terminal alkenes

The mixed diboron compounds **582**–**586** have been synthesised and characterised by Kleeberg,[160,161] while Yoshida has shown the synthesis of diboron **587**;[162] however, they have not been shown to have synthetic applications and so will not be discussed futher (Figure 6).

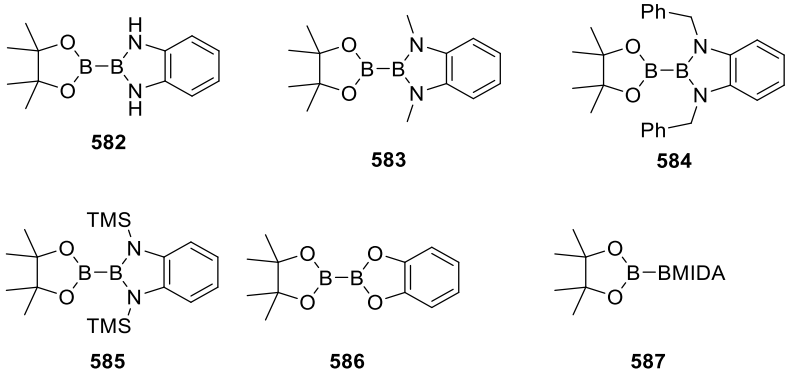
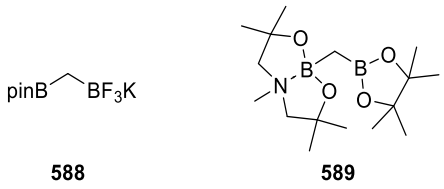


Figure 6 Literature known mixed diboron species

Results and discussion

Previous work

Previous work within the group towards the synthesis of a methylene linked differentially protected mixed diboron species targeted compounds **588** and **589** (Figure 7). In the case of mixed diboron **588**, one boron moiety is protected as the trifluoroborate salt, in which the coordination sphere of the boron atom is saturated and is therefore not electrophilic. The protecting group in mixed diboron **589** is derived from 1,1'-(methylazanediyl)bis(2-methylpropan-2-ol) and resembles the MIDA boronate, where the carbonyl groups have been replaced with geminal dimethyl groups. This alteration removes both the unprotected carbonyl groups and the enolisable protons that prevent the MIDA boronate being suitable reagent in lithiation−borylation reactions. Unfortunately, **588** was insoluble in ethereal solvents and **589** decomposed upon chromatography, thus rendering both unsuitable.

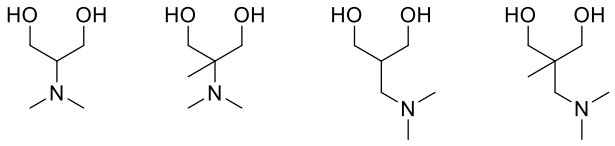


588 **589**

Figure 7 differentially protected diboron reagents that were synthesised by previous group members and shown in to unsuitable

Development of diol ligands

We started our investigation with diols **590**–**593** (Figure 8), which bear resemblance to the MIDA boronate in that they form a dioxaborylcycle when bound to boron and donate electron density via a tethered nitrogen atom. Unlike the MIDA boronate the tethered nitrogen atoms are exocyclic to the dioxaboryl ring.



590 **591** **592** **593**

Figure 8 Aminediol ligands **590**–**593**

For diols **590**–**593** to be suitable protecting groups their corresponding dioxaborylcycles (**594**–**597**) must adopt a boat conformation to place the nitrogen atom in the correct position to donate to the boron atom (Figure 9). In the chair conformation, the tethered nitrogen atom will be placed in an equatorial position and point into space. A methyl

group α to nitrogen, as in **591**, would be axial in a chair conformation. We rationalised that this would destabilise the chair conformation and promote formation of the boat. Further modifications could be made by introducing a methylene link between the nitrogen atom and dioxaboryl ring, thus potentially placing nitrogen atom in a better position to form a dative bond with the boron centre, such as in **596** and **597**.

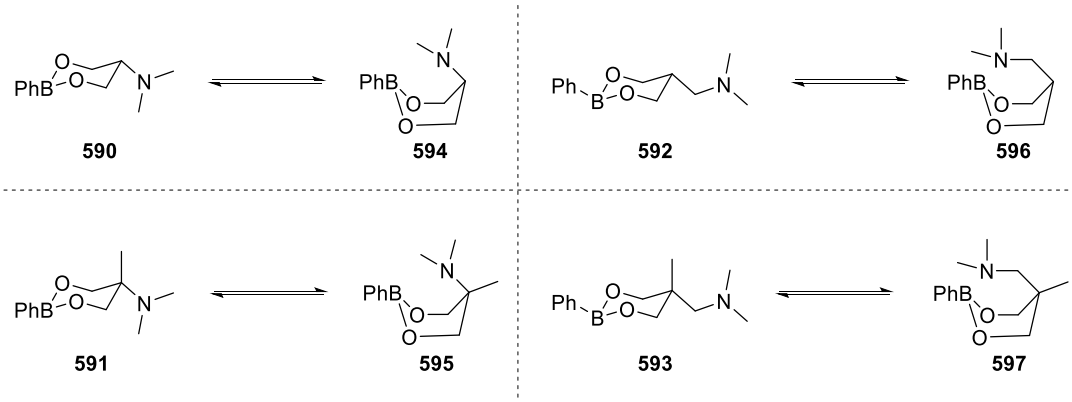
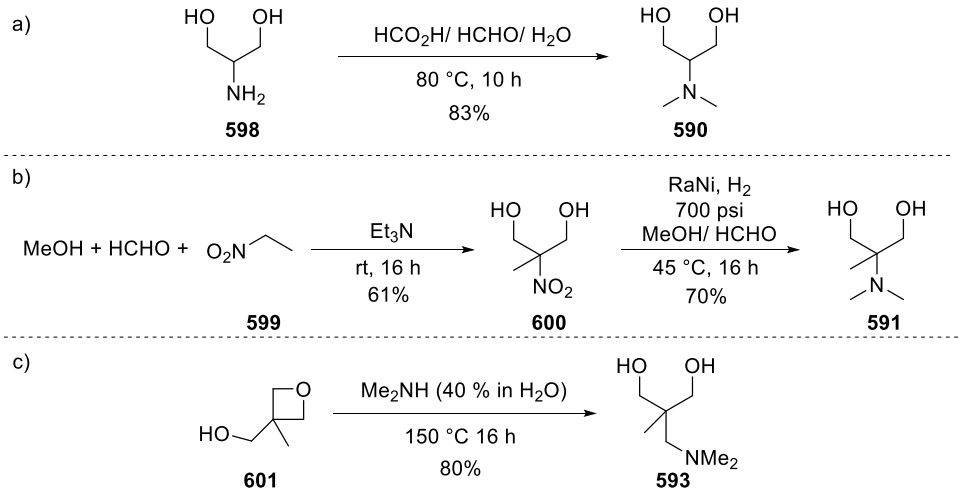


Figure 9 Conformational analysis of aminediol ligands bound to boron

*Synthesis of aminodiols **590**, **591** and **593***

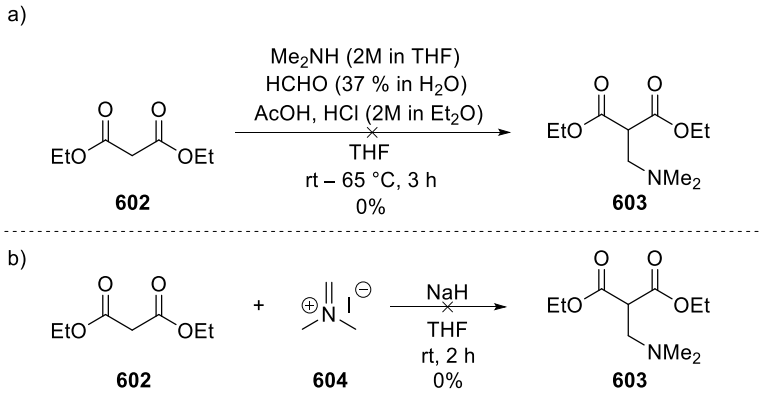
The synthesis of diol **590** was achieved in a simple one-step dimethylation of serinol (**598**) (Scheme 132a). The product was obtained in high yield after heating at 80 °C for 10 h, without the need for additional purification. Diol **591** was synthesized in two-steps from nitroethane (**599**) (Scheme 132b). The initial step proceeded through the double addition of formaldehyde to the enolate of nitroethane to form intermediate **600**, which was obtained as a white solid. Compound **600** was then subjected to a high-pressure hydrogenation with RaNi, followed by in situ dimethylation of the formed amine to afford the desired ligand in high yield. Diol **593** was synthesized in one-step in high yield through high-temperature alkylation of oxetane **601** with dimethylamine (Scheme 132c).



Scheme 132 Synthesis of aminodiols **590**, **591** and **593**

*Attempted synthesis of diol **592***

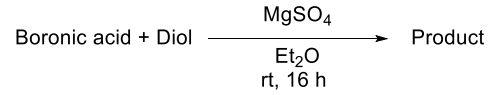
It was hoped that diol **592** could be synthesized in a two-step procedure from diethylmalonate (**602**) by an initial Mannich reaction to yield intermediate **603**, followed by reduction of the diester to yield the desired diol. Upon evaluation of the literature, it was not possible to find an example of this Mannich reaction using dimethyl amine, although the same transformation with dibenzylamine was reported.[163] Attempting this reaction with dimethylamine resulted in a complex mixture, from which **603** could not be isolated (Scheme 133a). In light of this failure the route was altered to use Eschenmoser's salt (**504**) as this was predicted to be a more direct and facile route to **603** (Scheme 133b). Unfortunately, this method also did not yield the product, and again many new spots were observed by TLC analysis. Due to the unpredicted difficulty in the synthesis of diol **592** it was removed as a target.



Scheme 133 Failed attempt to synthesise intermediate **603**

Complexing diols to phenylboronic acid and evaluation of ^{11}B NMR chemical shift values

Phenylboronic acid was chosen as a model substrate to investigate the properties of aminodiols **590–593** when complexed to boron. Complexation was achieved by stirring the requisite diol with phenylboronic acid in Et_2O overnight in the presence of flame-dried $MgSO_4$ (Table 14).



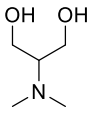
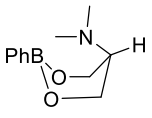
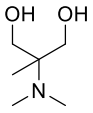
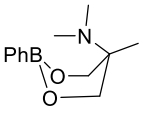
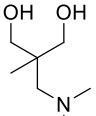
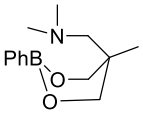
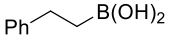
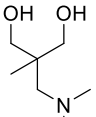
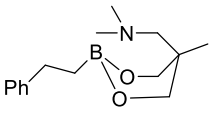
Entry	Boronic acid	Diol	Product
1	$PhB(OH)_2$	 **590**	 **594**
2	$PhB(OH)_2$	 **591**	 **595**
3	$PhB(OH)_2$	 **593**	 **597**
4		 **593**	 **605**

Table 14 Transesterification of ligands **590**–**593** to simple boronic acids

$MgSO_4$ was present to remove water and drive the equilibrium in favour of products. In each case, the expected product was formed, as according to ^1H NMR analysis of the crude mixture. As ^{11}B NMR chemical shift is controlled by the electron occupancy of the vacant boron orbital,[164,165] evaluation of the efficiency of protection afforded by each of the ligands can be evaluated by considering the ^{11}B NMR chemical shift relative to that of a pinacol boronic ester (~33 ppm) (Figure 10). As a reference, MIDA boronate **606** has a ^{11}B shift of 10.8 ppm.[166] In the case of compound **594**, the ^{11}B chemical shift is only slightly more upfield than that of a boronic acid pinacol ester. This suggests that the nitrogen atom is poor at donating electron density into the vacant boron orbital, which suggests that either a high proportion of the population is in the chair conformation, or that the nitrogen atom is too far from the boron atom to form a dative bond. As predicted,

introduction of a methyl group α to the nitrogen atom did indeed lower the ^{11}B chemical shift, as shown by compound **595**, thus suggesting that destabilisation of the chair conformation aids in the formation of a dative bond between nitrogen and boron atoms. Introduction of a methylene link between the nitrogen atom and the ring further reduced the ^{11}B chemical shift to 3.83 ppm in compound **597**, which is analogous to a boronate complex. This suggests a formal bond between the boron and nitrogen atoms and shows that the presence of a methyl substituent at the tip of the boat and a methylene linker between the nitrogen atom and the ring place the nitrogen atom in the optimal position to donate electron density. Unfortunately, boronic esters **594** and **595** were not stable to flash column chromatography and decomposed upon chromatographic purification to phenylboronic acid and the corresponding diol. Interestingly, boronic ester **597** proved to be stable but immobile on silica gel. To combat this, the boronic acid coupling partner was changed to phenethylboronic acid, which is slightly more lipophilic and should elute through silica gel more readily. Boronic ester **605** again showed a ^{11}B NMR chemical shift in the region of a boronate complex, suggesting a formal nitrogen to boron dative bond. Boronic ester **605** proved to also be immobile on silica gel, even in very polar eluents (mobile phases consisting of MeOH/DCM, MeOH/NH_3/DCM, THF and CH_3CN/Et_2O were trialled). This immobility is puzzling as the ^{11}B NMR chemical shifts suggest a formal N−B bond. The origin of this immobility may be due to breaking of the N−B bond in solution, thus allowing coordination of the nitrogen atom to silica gel. Alternatively, a strong N−B bond may cause weakening of one of the B−O bonds, generating a partial negative charge on the oxygen atom that may interact with silica gel. Owing to poor compatibility with silica gel it was decided that these ligands would not be suitable protecting groups in lithiation–borylation reactions and were discarded as targets.

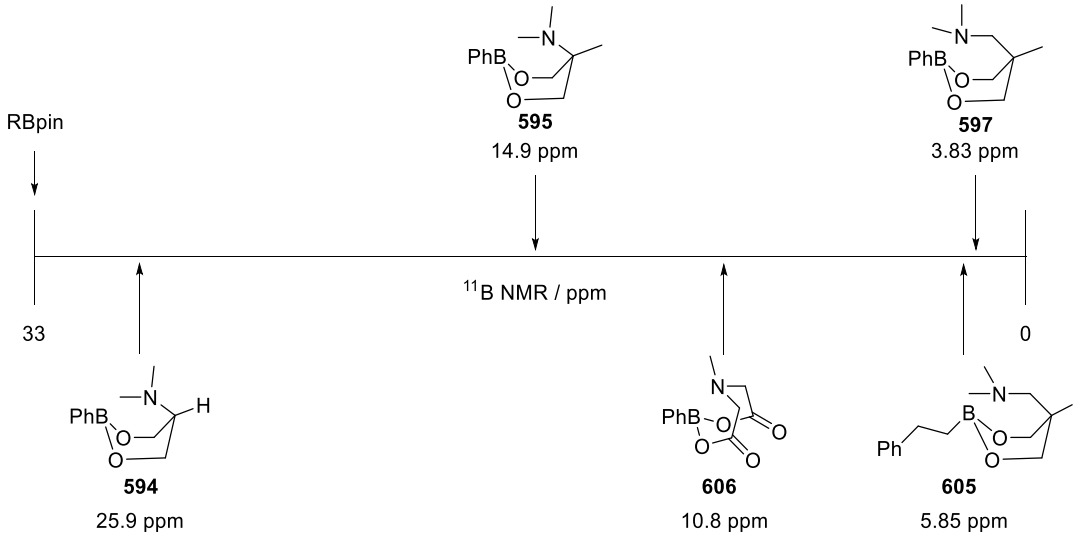


Figure 10 ^{11}B NMR chemical shifts of compounds **594**, **595**, **597** and **605**

Development of diamine ligands

Our attention next turned to groups that would protect a boronic ester through inductive donation of electron density. These compounds would be related to Suginome's DAN ligand. The diamines **607** and **608** had previously been synthesised in the group and had decomposed upon chromatographic purification when coordinated to a boronic ester. Diamine **609** was selected as the next candidate to test as a boronic ester protecting group (Figure 11).

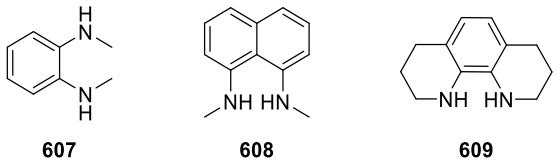
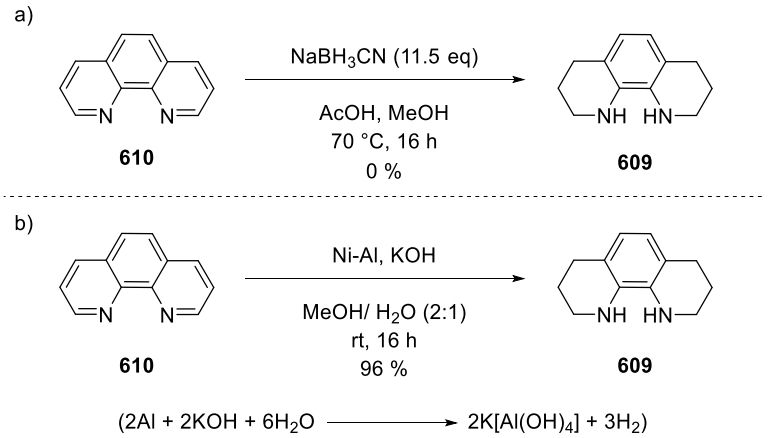


Figure 11 Diamines **607**, **608** and **609**

*Synthesis of diamine **609***

On evaluation of the literature it was found that diamine **609** could be accessed through reduction of 1,10-phenanthroline (**610**).[161,162] Treatment of **610** with sodium cyanoborohydride yielded many spots, as determined by TLC analysis, of which none could be identified as the desired product. (Scheme 134a). The route was therefore altered to use 50% Ni−Al alloy, which proceeded in almost quantitative yield at ambient temperature after stirring for 16 h (Scheme 134b). Mixing aluminium with aqueous hydroxide generates a tetra-hydroxy aluminium complex and dihydrogen, which acts as the reductant in the presence of RaNi. The reaction is performed by dissolving 1,10-phenanthroline (**610**) and KOH pellets in MeOH and H_2O, followed by the portion

wise addition of Ni−Al alloy. As the alloy is added, the reaction mixture turns from colourless to dark green, and starts spontaneously refluxing. Cooling the reaction mixture at this point was found to be detrimental to the yield (58%), whereas almost quantitative yield was obtained when the reaction refluxed. This procedure allowed **609** to be obtained without the need for chromatographic purification. The product (**609**) was obtained as a bright yellow solid, which was not bench stable and decomposed over a few days when left open to air. Storage under nitrogen in the freezer led to ligand **609** being viable for several months.

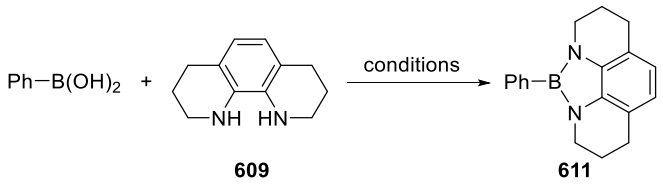


Scheme 134 Reduction of 1,10-phenanthroline (**610**)

*Complexing diamine **609** to a simple boronic acid*

We next sought to complex ligand **609** to a simple boronic acid to evaluate its stability to silica gel. Unfortunately, this process was not as facile as in the case of diols **590**, **591**, and **593** (Table 15). An initial attempt involved stirring phenethyl boronic acid with diamine **609** in Et_2O at room temperature overnight in the presence of one equivalent of flame–dried $MgSO_4$ (Table 15, entry 1). Unfortunately, TLC analysis showed that no reaction had occurred and both starting materials were recovered. It has been shown that Fe(III) species can be used to catalyse the ligation of Suginone's DAN ligand to simple boronic acids in the presence of water and imidazole in yields of up to 89%.[169] Although the DAN ligand contains two primary amines and so should be an easier coupling, we attempted to adopt this methodology to diamine **609** (Table 15, entry 2). TLC analysis of the reaction mixture again showed that no reaction had occurred and the starting materials were recovered. Finally, the product was obtained as a purple solid by refluxing the components overnight in toluene under Dean−Stark conditions in the presence of a

catalytic amount of DBU (Table 15, entry 4). Although the reaction proceeded in the absence of DBU (Table 15, entry 5), this was detrimental to the yield. Even more gratifyingly, the product was both mobile on, and stable to silica gel chromatography and was isolated using a gradient of 5% EtOAc in petroleum ether.



609 **611**

Entry	Conditions	Yield / %
1	$MgSO_4$, Et_2O rt, 16 h	0
2	$FeCl_3$ (5 mol%) imidazole H_2O, CH_3CN rt, 3 h	0
3	DBU, PhMe 120 °C, 16 h	78
4	PhMe 120 °C, 16 h	38

Table 15 Ligation of **609** to phenylboronic acid

*Evaluation of protecting group ability of diamine **609***

As expected the ^{11}B chemical shift of **611** was more downfield than that of protected boronic esters **594**, **595**, **597** and **605**, owing to donation of electron density from the nitrogen atom through an inductive effect being a more subtle than dative donation (Figure 12). Despite this, the difference in chemical shift values (33 versus 26.5 ppm) of **611** and a pinacol boronic ester should be sufficient for discrimination by a carbenoid and so **611** was tested in a lithiation–borylation reaction.

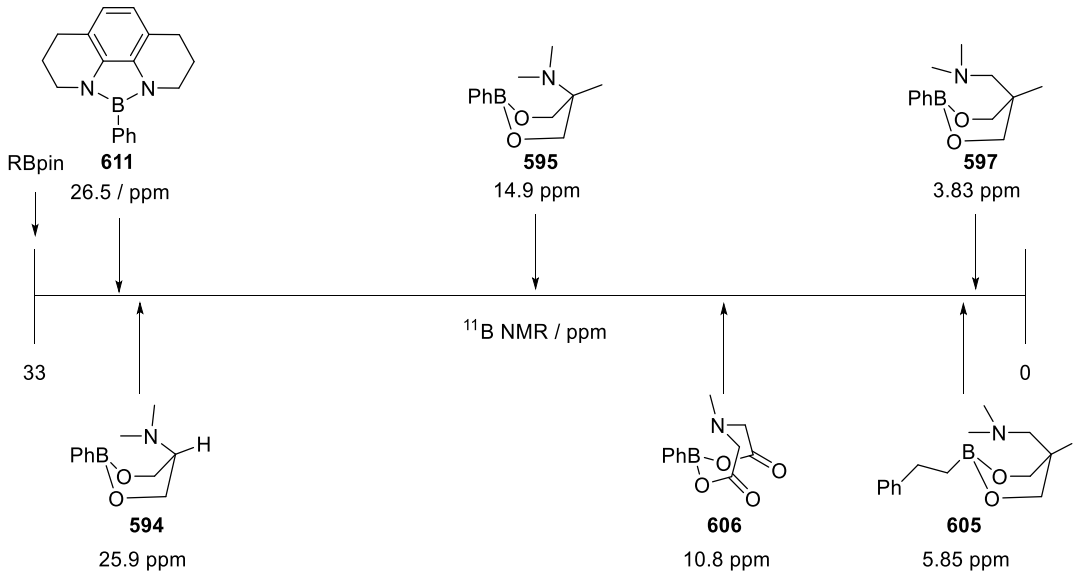
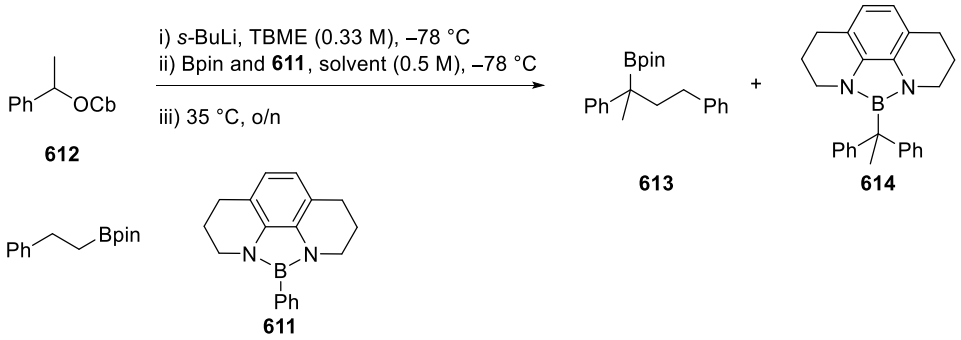


Figure 12 ^{11}B NMR shifts of compounds 611, **594**, **595**, **605** and **597**

Competition lithiation−borylation reaction

To test whether our designed diamine was indeed a boronic ester protecting group, a lithiation−borylation competition experiment was attempted using phenethylboronic pinacol ester and protected phenylboronic acid **611** (Scheme 135). If diamine **609** is a successful protecting group, the reaction should yield compound **613** exclusively. Formation of organoboron **614** would indicate that protected boronic acid **611** is electrophilic enough to be intercepted with a lithiated carbenoid and so would not be a suitable protecting group. The lithiation of secondary benzylic carbamate **612** was performed in TBME at –78 °C in the absence of a coordinating diamine. Phenethyl boronic ester and **611** were to be added together as a solution in TBME at –78 °C after a lithiation period of 2 h. Unfortunately, protected boronic acid **611** was completely insoluble in both TBME and Et_2O and was only partially soluble in toluene. Owing to this poor solubility the reaction was not completed as it was not possible to determine the amount of **611** being added.



Scheme 135 Competition lithiation−borylation experiment

The value of the ^{11}B NMR chemical shift of **611** gave us cause to assume that it would be a suitable protecting group, and was carried through to the synthesis of the mixed diboron compounds **615** and **616** in the hope that they would be soluble in ethereal solvents (Figure 13).

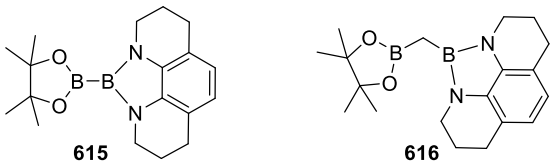
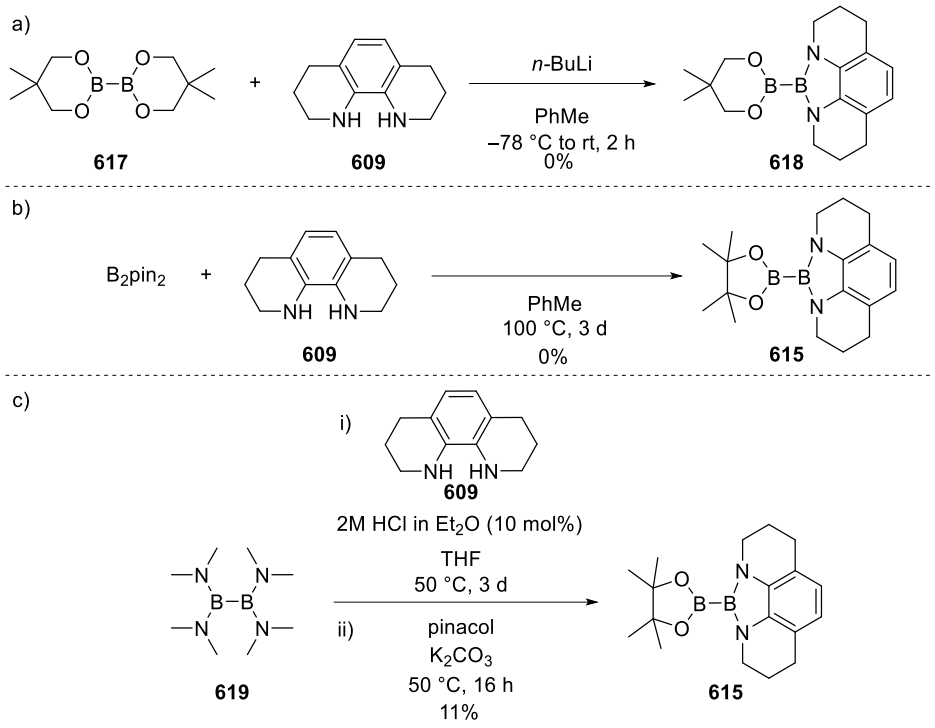


Figure 13 Mixed diboron compounds **615** and **616**

*Synthesis of mixed diboron **615***

Initial attempts to coordinate diamine **609** to $B_2(OH)_4$ by refluxing the mixture in toluene with catalytic amounts of DBU were unsuccessful. A more forceful approach was therefore attempted where diamine **609** was lithiated with *n*-BuLi followed by the addition of B_2neo_2 (**617**). The neopentylglycolato group could then be transesterified with pinacol to yield the desired mixed diboron (**615**). Upon addition of *n*-BuLi a colour change was observed from pale yellow to bright orange, suggesting lithiation had occurred; however, the ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture that did not appear to contain product (Scheme 136a). Ken has shown that mixed diboron compound **567** could be made by heating diaminonaphthalene with B_2pin_2 in toluene for a prolonged period of time at 100 °C.[170] We sought to emulate this procedure to afford our desired diboron compound (**615**). Unfortunately, no reaction occurred and both starting materials were recovered after heating at 100 °C in toluene for 3 d (Scheme 136b). Finally, the synthesis of **615** was achieved using a procedure developed by Suginome for the synthesis of **567** (Scheme 136c).[155] Freshly distilled tetrakis(dimethylamino)diboron (**619**) and diamine **609** were heated at 50 °C for 3 d in

anhydrous THF in the presence of a catalytic amount of anhydrous HCl. After this time, the reaction was basified with K_2CO_3 and pinacol was added. The reaction mixture was then stirred for a further 16 h at 50 °C, where after workup and purification, the desired product (**615**) was obtained in 11% yield as a white solid. Although this yield is low, enough material was obtained to investigate the reactivity of **615**. Efforts to optimise this process were put on hold pending the results of the investigation into the reactivity of **615**.

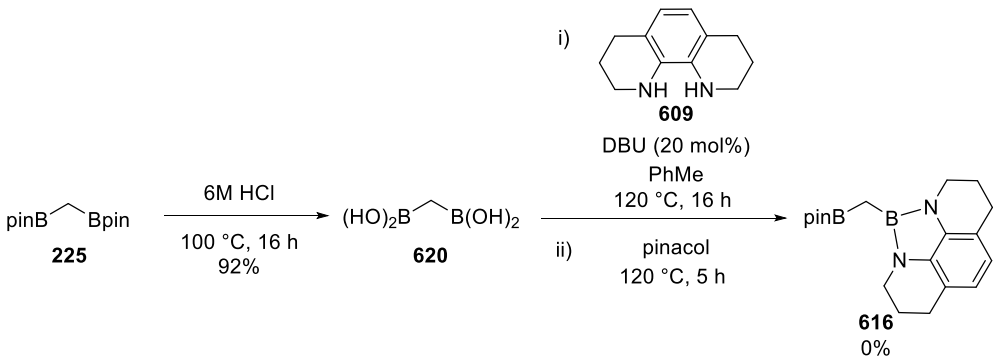


Scheme 136 Synthesis of mixed diboron componud **615**

*Synthesis of mixed diboron **616***

It was envisioned that the synthesis of mixed diboron **616** could be achieved through the sequential esterification of 1,1-bis(boronic acid) **620**, which was obtained through hydrolysis of diborylmethane (**225**) (Scheme 137). Bis(boronic acid) **620** was first heated at 120 °C in toluene with one equivalent of diamine **609** and a catalytic amount of DBU. Pinacol was then added and the reaction mixture heated for a further 5 h. Unfortunately, none of the desired product could be detected and **609** was re-isolated in almost quantitative yield. Diborylmethane (**225**) was isolated in approximately 22% yield, which was presumably generated through the double addition of pinacol to **620**. This result could be because pinacol is able to exchange with diamine **609**, or because bis(boronic acid)

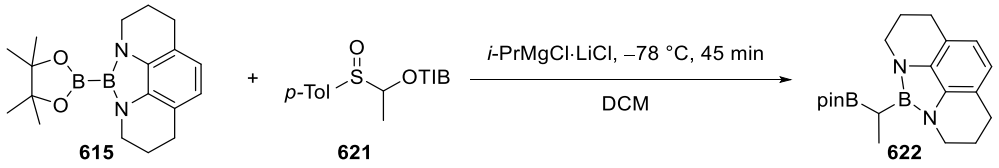
620 is inert to esterification with **609**. Due to the difficulties in synthesising **616**, its synthesis was put on hold while the properties of **615** were investigated.



Scheme 137 Attempted synthesis of mixed diboron **616**

*Homologation of mixed diboron **615** with sulfoxide **621***

With mixed diboron **615** in hand, it was possible to evaluate its behaviour in a lithiation−borylation reaction, the product of such a reaction would be a differentially protected 1,1-bis(boronic ester). To our dismay, **615** was insoluble in Et_2O, TBME, CPME and PhMe; however, it was completely soluble in DCM and so we tested a homologation between **615** and the carbenoid derived from sulfoxide **621** when using *i*-PrMgCl·LiCl as the metallating agent. Sulfoxide–magnesium exchange of **621** was achieved at –78 °C through addition of *i*-PrMgCl·LiCl to a mixture of **615** and **621**. After 45 min the reaction was heated to 35 °C for 16 h to promote 1,2-metallate rearrangement. Gratifyingly, a new spot was present by TLC analysis and formation of the desired product was supported by GCMS analysis; however, owing to the scale this reaction was performed on, **622** was not fully characterised (Scheme 138).



Scheme 138 Homologation of mixed diboron **615** with the carbenoid derived from sulfoxide **621**

Despite being in a very promising position, work on this project was stopped at this point. The reason for this was not related to the chemistry or a loss of interest in the project but will not be discussed further.

Conclusion

Throughout the preceding section efforts towards the design and synthesis of a novel boronic ester protecting group that is compatible with lithiation−borylation reactions have been discussed. Despite their facile installation, it was shown that the diol ligands **590**, **591** and **593** are not suitable owing to their unfavourable interaction with silica gel when coordinated to a simple boronic acids (Figure 14). Evaluation of the ^{11}B NMR chemical shift values of **590**, **591** and **593** bound to a simple boronic acid showed that each was competent at reducing the Lewis acidity of the boron atom to a greater or lesser extent. As predicted, diol **593** was a superior protecting group than diol **590**, a difference that is attributed partly to an axially dispositioned methyl group which destabilises the low energy chair conformer and a methylene linker that allows for more efficient lone pair donation from the nitrogen atom to the boron atom.

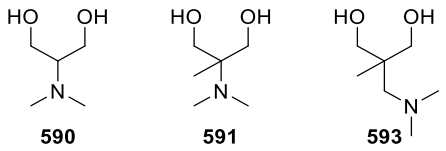


Figure 14 Unsuccessful diol protecting groups

It was found that reduction of 1,10-phenanthroline afforded diamine **609**, which once coordinated to a simple boronic acid displayed excellent stability and mobility on silica gel. An efficient procedure to coordinate diamine **609** to boronic acids has been shown. Synthesis of the mixed diboron **615** has been achieved, albeit in low yield, whereas the synthesis of **616** is still challenging. The poor solubility of **615** in ethereal solvents prevented its use in standard lithiation–borylation reactions; however, **615** has been shown to engage in a reaction with a magnesium carbenoid derived from the corresponding α-sulfinyl benzoate in DCM.

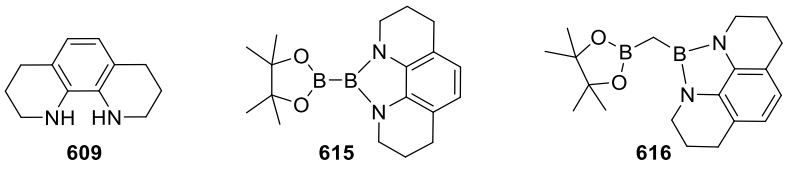


Figure 15 Compounds **609**, **615** and **616**

In conclusion, the foundations for the project have been laid. Diamine **609** has been identified as a suitable group to take forwards in the project and a method for its ligation to a boronic acid has been realised. The synthesis of diboron **615** has been achieved but

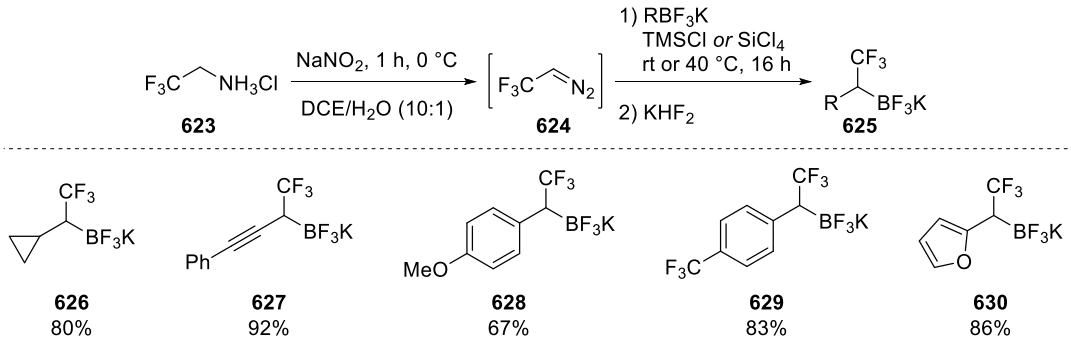
requires further optimisation to become synthetically useful. The next step is to test diboron **615** in diboration reactions with terminal alkenes and then to evaluate the secondary selective homologation of primary protected 1,2-bis(boronic esters).

Chapter 4: Towards a New Leaving Group in Lithiation–Borylation Reactions

Introduction

Formation of fluorinated boronic esters through boron homologation reactions

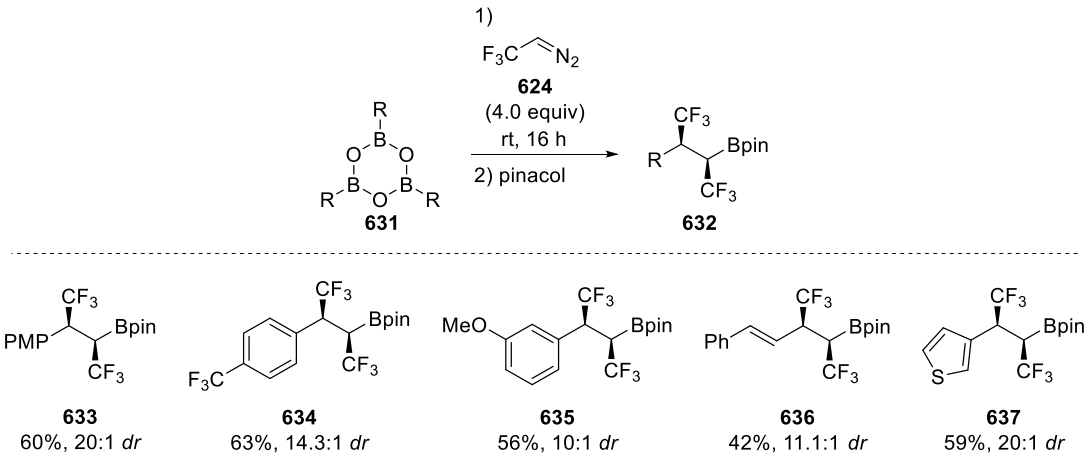
Molander has shown that 2,2,2-diazotrifluoroethane (**624**)—generated from ammonium salt **623** with $NaNO_2$—can be homologated with boronic acids or dihaloboranes to yield α-CF_3 trifluoroborates, such as **625**, after quenching the reaction with KHF_2 (Scheme 139).[171] The reaction could also be quenched with pinacol to yield the corresponding pinacol boronic esters; however, the α-CF_3 boronic esters were not stable and decomposed through auto-oxidation upon isolation. The substrate scope of the reaction was broad and tolerated a variety of α-CF_3 trifluoroborates that contained alkyl (**626**), propargyl (**627**), electron rich-, electron deficient- and heteroaromatic (**628**, **629** and **630**) side chains in excellent yield. The success of the reaction was attributed to the use of a very good leaving group (N_2), which promoted a rapid 1,2-metallate rearrangement and thus suppressed decomposition of the boronate complex.



Scheme 139 Homologation of dihaloboranes with 2,2,2-trifluorodiazoethane

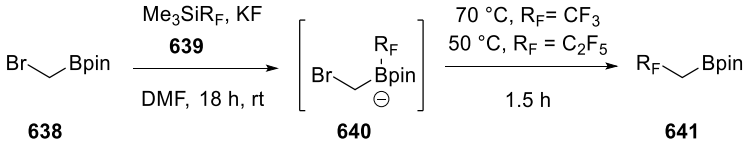
Interestingly, using the potassium trifluoroborate as limiting reagent did not lead to more than trace amounts of over homologation. However, when using a boroxine, such as **631**, the double homologation product was obtained as the major product (Scheme 140).[172] Using 4.0 equiv of 2,2,2-trifluorodiazoethane (**624**) proved to be optimum and resulted in the formation of bis(homologated) products (**632**) in good yield and *dr*. The substrate scope was again broad and tolerated substrates containing electron rich- and electron deficient aryl groups (**633** and **634**). The reaction didn't proceed with *ortho*-substituted aromatics due to steric effects; however, *meta*-substituted aromatics were tolerated (**635**).

One example of a substrate containing a heteroaromatic group was given (**637**). The inclusion of others was limited by the availability of the heteroaromatic boroxines, which were unstable and decomposed by protodeboronation upon heating. Evaluation of the crystal structure of compound **634** showed the relative configuration to by *syn*.



Scheme 140 Double homologation of cyclic boroxines with 2,2,2-trifluorodiazoethane

Dilman has shown that migration of a CF_3 or C_2F_5 group attached directly to boron is possible with bromide as a leaving group when forcing conditions are used (Scheme 141).[173] Activation of silyl species **639** with KF afforded a nucleophilic ate complex that transfered the R_F group to the boron atom of **638**, thus forming boronate complex **640**. Heating the reaction mixture affords migration, which furnished homologated fluorinated boronic ester **641**. As with Molander's homologation, the success of this transformation is attributed to the use of an excellent leaving group.

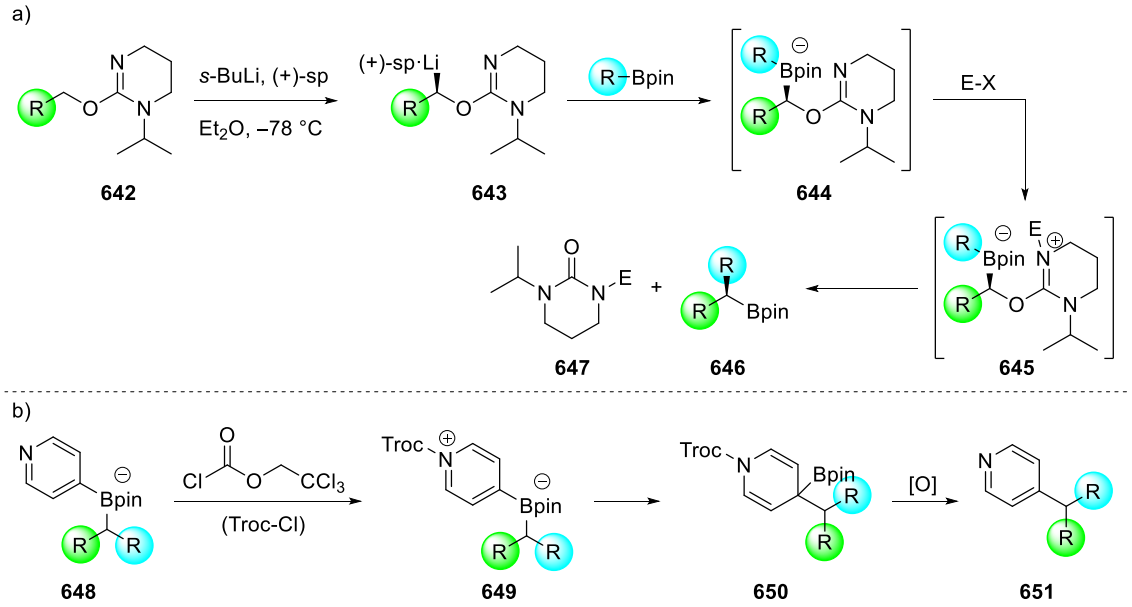


Scheme 141 Migration of a perfluoroalkyl group using bromide as a leaving group

Project Proposal

A major limitation of lithiation–borylation reactions is that when the boronic ester or carbenoid bears an electron withdrawing[168,169] or mesomerically stabilising[36,37] substituent, reversible fragmentation of the boronate complex occurs in preference to 1,2-migration, which results in reduced *ee* values or decomposition of the sensitive organolithium reagents *in situ*. This phenomenon limits the scope of lithiation–borylation reactions and precludes the formation of boronic esters bearing interesting or medicinally

relevant substituents—such as (per)fluorinated alkyl groups—with this methodology. We envisaged that employing a new leaving group, which is superior to the standard carbamate or benzoate, would promote the desired 1,2-migration over reversibility and enable (per)fluorinated boronic esters to be accessed with this methodology. However, as the nucleofugality of the leaving group is increased the nucleophilicity of the lithiated species is reduced, disfavouring boronate complex formation and increasing the propensity of reversibility. The ideal moiety would therefore be a very poor leaving group—to maximise the nucleophilicity of the carbenoid—until activated with a suitable reagent. In addition, the leaving group must be able to coordinate to the *s*-BuLi/(+)-sparteine complex and direct lithiation. We propose the use of *O*-alkyl isoureas as carbenoid precursors. Treatment of pro-chiral carbenoid precursor **642** with a combination of (+)-sparteine and *s*-BuLi should result in asymmetric deprotonation of the pro-*R* proton through coordination of the nitrogen atom lone pair of the isourea to form lithiated species **643**, which is predicted to be more nucleophilic than the complementary carbamate. Quenching this carbenoid with a boronic ester should result in the formation of boronate complex **644**. Activation of the isourea with an electrophile should then form a very good leaving group, which should trigger migration at a temperature below where the boronate complex fragments unproductively to starting material, thus furnishing homologated boronic ester **646** and urea derivative **647**. The isopropyl group on the nitrogen atom of the isourea is designed to block the attack of the sp^2 carbon of the isourea by *s*-BuLi (Scheme 142a). This activation strategy has been used previously within our group in a metal-free cross-coupling of a boronic ester and pyridine. Upon addition of Troc-Cl, boronate **648** was acylated at the nitrogen atom, thus facilitating 1,2-migration.[176] The boronic ester was then oxidised and eliminated to yield the cross-coupled pyridine (**651**) (Scheme 142b).



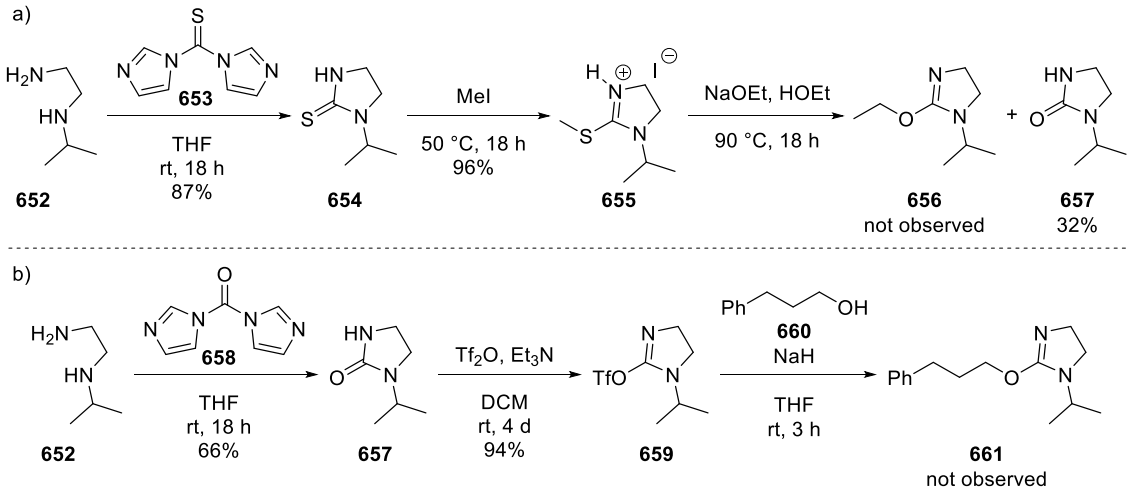
Scheme 142 The proposed use of isoureas as the leaving group in lithiation–borylation reaction

Results and Discussion

Synthesis of isoureas

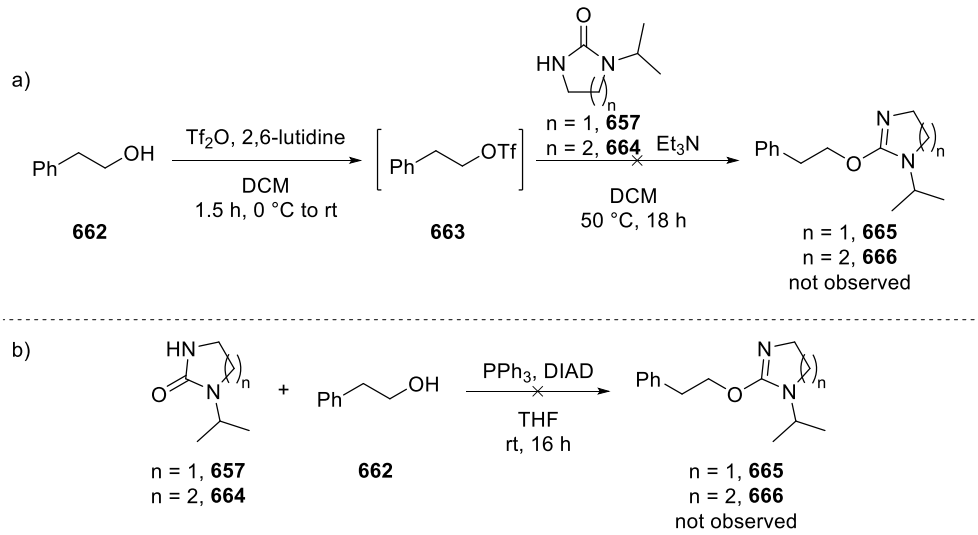
We first targeted the synthesis of 5-membered cyclic isourea **656** through an adaption of the procedure reported by Jones.[177] Cyclic thiourea **654** was accessed in high yield through the addition of thiocarbonyldiimidazole (**653**) to *N*-isopropyl ethylenediamine (**652**). Refluxing cyclic thiourea **654** in neat iodomethane afforded methyl isothiourea **655** in almost quantitative yield. Treatment of **655** with sodium ethoxide in EtOH did not provide any of the desired isourea (**656**), instead cyclic urea **657** was isolated exclusively. The *N*-isopropyl group of **656** was designed to be a steric shield to prevent attack of the sp^2 carbon of the isourea by *s*-BuLi and so it is plausible that the *N*-isopropyl group effectively shields this position and prevents substitution with EtOH. However, urea **657** is presumably formed through the attack of **655** by adventitious water. Because the yield of urea **657** is poor, an argument could be made that the *N*-isopropyl group is a good enough steric shield to effectively block the attack of EtOH, but is only large enough to partially inhibit the attack of water (Scheme 143a). We next sought to promote the desired transformation by incorporating a superior leaving group (Scheme 143b). Treatment of cyclic urea **657** with triflic anhydride and Et_3N gave triflate **659** in 94% yield after stirring at ambient temperature for 4 d. Surprisingly, no reaction was observed between **659** and the alkoxide derived from alcohol **660**, as determined by TLC analysis. This result bolstered the idea that the *N*-isopropyl group is too sterically demanding to allow for substitution at this position. We therefore aimed to use urea **657** as the nucleophile to

afford an isourea, such as **661**.



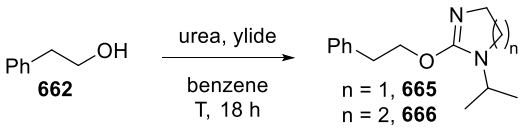
Scheme 143 Attempted syntheses of isoureas **656** and **661**

Triflate **663** was formed *in situ* by addition of triflic anhydride and 2,6-lutidine to phenethyl alcohol (**662**). After 1.5 h complete conversion of alcohol **662** to a new apolar spot was observed by TLC analysis. To this was added a solution of urea **657** or **664** and triethylamine in DCM. The resulting mixture was heated to 50 °C for 18 h. Remarkably, triflate **663** was stable under these conditions as neither **663** nor ureas **657** or **664** were consumed, as determined by TLC analysis (Scheme 144a). Ureas **657** and **664** were also inert under Mitsunobu conditions as no conversion of either was observed after stirring in the presence of DIAD and PPh_3 for 16 h, as determined by TLC analysis (Scheme 144b). The origin of this lack of reactivity stems from the low acidity of the urea N-H proton. DIAD is known to deprotonate protons with pK_a values of up to 15; however, the pK_a of the urea N-H proton is predicted to be between 19 and 26.[178] Instead of DIAD, Tsunoda proposes the use of phosphoranes as more reactive Mitsunobu reagents, specifically (cyanomethylene)trimethylphosphorane (CMMP) (**667**) and (cyanomethylene)tributylphosphorane (CMBP) (**668**), which can promote reactivity in substrates with pK_a values of up to 23.4.[179–183]



Scheme 144 Attempted synthesis of isoureas **665** and **666** using urea **657** and **664** as the nucleophile

The reaction was repeated using Tsunoda's methodology (Table 16). Urea **657** was first reacted with CMMP (**667**) in benzene in a sealed pressure tube at 100 °C for 18 h, which resulted in a complete lack of reactivity and the re-isolation of **657** (Table 16, entry 1). The reaction was repeated at 150 °C (Table 16, entry 2); however, these conditions also did not promote reactivity. Switching to the more reactive phosphorane (CMBP (**668**), Table 16, entry 3) also resulted in no reactivity and both **657** and **662** were re-isolated. Finally, we attempted to utilize 6-membered urea **664** but again no reactivity was observed (Table 16, entry 4).



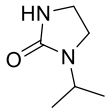
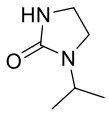
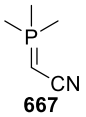
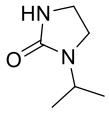
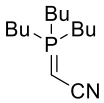
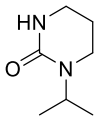
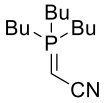
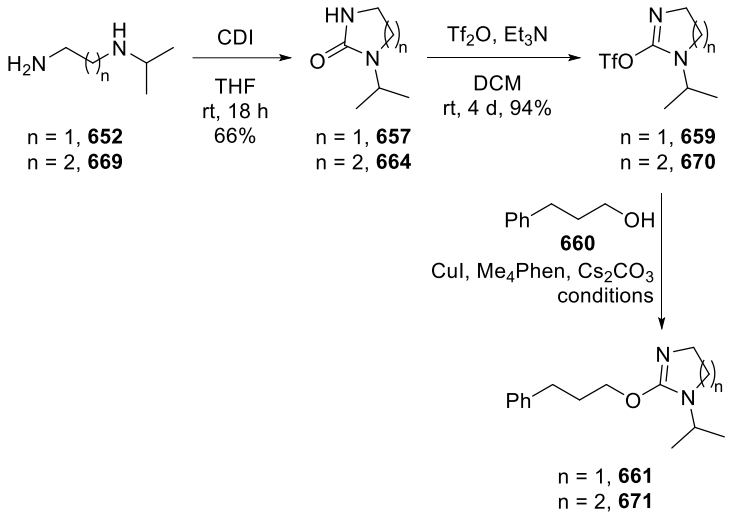
Entry	Urea	Ylide	T / °C	Comment
1		 **667**	100	No consumption of SM
2		 **667**	150	No consumption of SM
3		 **668**	100	No consumption of SM
4		 **668**	150	No consumption of SM

Table 16 Attempted synthesis of **665** and **666** using phosphoranes **667** and **668**

Our attempts to synthesise isoureas **661** and **671** finally came to fruition when applying a copper-catalysed Ullman coupling between triflate **659** or **670** and alcohol **660**, as described by Buchwald (Table 17).[184] Treatment of triflate **659** with CuI, 3,4,7,8-tetramethyl-1,10-phenathroline and Cs_2CO_3 in toluene at 110 °C for 48 h yielded isourea **661** in 17% yield (Table 17, entry 1). An improvement in yield was achieved by heating at 200 °C under microwave irradiation for 8 hours in xylenes (Table 17, entry 2). Complementary results could be achieved when using six-membered triflate **670** under the same conditions (Table 17, entry 3). Finally, isourea **671** could be obtained in 49% yield by performing the reaction under an atmosphere of air (Table 17, entry 4). With desired isoureas **661** and **671** in hand we next sought to test their amenability to asymmetric lithiations with (+)-sparteine and *s*-BuLi.



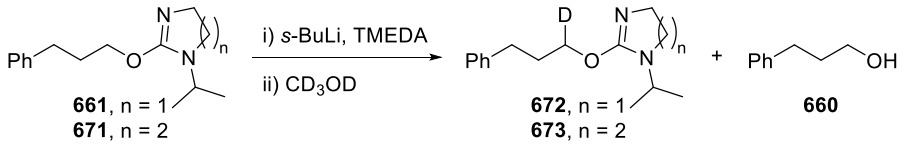
Entry	n	Heating	T / °C	t / h	Solvent	Reaction atmosphere	Yield / %
1	1	conventional	110	48	PhMe	N_2	17
2	1	microwave irradiation	200	8	xylenes	N_2	36
3	2	microwave irradiation	200	8	xylenes	N_2	34
4	2	microwave irradiation	200	6	xylenes	air	49

Table 17 Optimisation of the copper catalysed cross-coupling reaction between triflates **659** and **670** and alcohol **660**

*Lithiations of isoureas **661** and **671***

The lithiation of isoureas **661** and **671** was next evaluated through lithiation–deuteration studies (Table 18). Initially 5-membered cyclic isourea **661** was subjected to 1.1 equiv of *s*-BuLi and 1.1 equiv of TMEDA for 6 hours at −78 °C in Et_2O. Following this lithiation period, the reaction was quenched at −78 °C with CD_3OD and the mixture warmed to ambient temperature (Table 18, entry 1). Crude TLC analysis showed the presence of 3 spots, which corresponded to starting isourea **661**, alcohol **660** and a baseline spot, which wasn't characterised. The presence of alcohol **660** was presumably caused by attack of *s*-BuLi at the sp^2-hybridised carbon atom of isourea **661**. The baseline spot was therefore assumed to be diamine by-products of this process. ^{1}H NMR analysis of the crude reaction mixture revealed that no deuteration had occurred. This result was surprising as earlier difficulties in synthesising isourea **661** had led us to believe that the isopropyl group would be an effective steric block of the sp^2-hybridised carbon atom. However, as complete conversion of isourea **661** to alcohol **660** had not occurred we continued our attempts to optimise the lithiation of this substrate. 6-membered cyclic isourea **671** was then subjected to the same conditions (Table 18, entry 2); however, the presence of

alcohol **660** was again detected by TLC and ^{1}H NMR analysis and no deuteration was observed. Increasing the temperature to −60 °C did not allow for deuteration in the case of 5-membered cyclic isourea **661** (Table 18, entry 3); however, 38% deuteration of 6-membered cyclic isourea **671** was observed when also increasing the equivalents of *s*-BuLi and TMEDA (Table 18, entry 4). Unfortunately, elimination of alcohol **660** was persistent under these conditions. Changing solvent to CPME had a positive effect for 6-membered cyclic isourea **571** and gave 50% deuteration; however, 5-membered cyclic isourea **661** remained resistant to lithiation (Table 18, entries 5 and 6). It is known that increasing the number of equivalents of diamine in relation to *s*-BuLi is beneficial to the lithiation of challenging substrates.[185] Attempting the lithiation with 1.5 equivalents of *s*-BuLi and 6.0 equivalents of TMEDA was still not sufficient to afford lithiation of 5-membered cyclic isourea **661** (Table 18, entry 7). To our surprise, applying these conditions to 6-membered cyclic isourea **671** resulted in poorer lithiation than previously observed, and when changing the solvent back to Et_2O, the level of lithiation was poorer still (Table 18, entries 8 and 9). Finally, lithiation was attempted with inverse addition; specifically, the addition of 6-membered cyclic isourea **671** to a preformed complex of *s*-BuLi and (+)-sparteine (Table 18, entry 10). As the complex of *s*-BuLi and (+)-sparteine is required to afford lithiation in the corresponding benzoates and carbamates, it was predicted that preforming this complex would enhance lithiation and reduce elimination of alcohol **660**. Unfortunately, this was not the case and complete conversion of 6-membered cyclic isourea **671** to alcohol **660** was observed under these conditions.



661, n = 1
671, n = 2

672, n = 1
673, n = 2

660

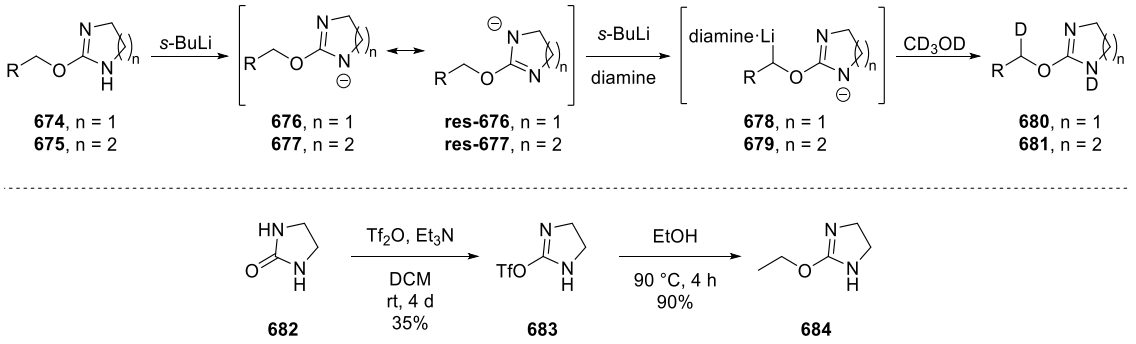
Entry	n	Li time / h	T / °C	*s*-BuLi eq	TMEDA eq	Solvent	D incorp. / %
1	1	6	–78	1.1	1.1	Et_2O	0
2	2	5	–78	1.1	1.1	Et_2O	0
3	1	6	–60	1.1	1.1	Et_2O	0
4	2	5	–60	1.5	1.5	Et_2O	38
5	1	5	–60	1.5	1.5	CPME	0
6	2	5	–60	1.5	1.5	CPME	50
7	1	5	–60	1.5	6.0	CPME	0
8	2	5	–60	1.5	6.0	CPME	24
9	2	5	–60	1.5	6.0	Et_2O	8
10 inverse add^n	2	5	–60	1.5	1.7 (+)-sp	Et_2O	0*

* complete conversion of starting material to alcohol **XX**

Table 18 Lithiation–deuteration studies of isoureas **661** and **671**

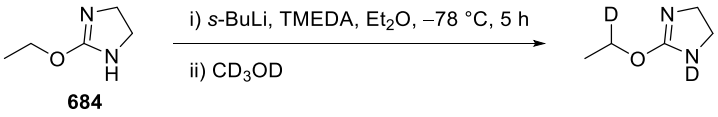
These results revealed two issues that needed to be addressed. The first is that attack of the sp^2 carbon atom by *s*-BuLi is occurring and that a new method of preventing this will need to be identified. The second is that lithiation is not occurring. Simply increasing the steric bulk of the isopropyl group was predicted to be sufficient to prevent attack of *s*-BuLi and elimination of alcohol **660**; however, absence of lithiation was expected to persist. As pre-coordination of the *s*-BuLi/diamine complex with the N atom lone pair of the isourea must occur, it was predicted that strengthening this interaction would aid lithiation. Both difficulties could plausibly by solved by using an electronic effect rather than a steric effect to protect the sp^2-hybridised carbon atom of the isourea (Scheme 145). Treatment of isourea **674** or **675** with one equivalent of *s*-BuLi would afford anion **676** or **677**, respectively. This anion would be stabilised through resonance, thus lowering the electrophilicity of the sp^2 carbon atom. In addition, resonance forms ***res*-676** and ***res*-677** have a full negative charge at the directing nitrogen atom, thus aiding in formation of a pre-coordination complex. Addition of a further equivalent of *s*-BuLi and a diamine should afford lithiation at the desired position, the resulting carbanion then being quenched by an electrophile (Scheme 145). Synthesis of ethyl isourea **684** was achieved in a two-step process starting from cyclic ureas **682.** Treatment of **682** with triflic

anhydride and triethylamine in DCM afforded triflate **683** in moderate yield. Refluxing in ethanol for 4 h afforded desired isourea **684** (Scheme 145).



Scheme 145 Proposed electronic protection of isourea **684**

Lithiation of isourea **684** was first attempted by adding an excess of *s*-BuLi (Table 19). Slow addition of 2.1 equiv of *s*-BuLi to isourea **684** in the presence of 2.1 equiv of TMEDA at −78 °C for 5h did not afford deuteration (Table 19, entry 1). Ethanol, a potential side product, is volatile and so was not detected after removal of solvent; however, only 41% of non-deuterated **684** was recovered, suggesting that decomposition of some sort had occurred. To counter this, it was decided to first add one equivalent of a non-nucleophilic base to form the desired anion, followed by the addition of *s*-BuLi (Table 19, entry 2). LiHMDS was chosen as the non-nucleophilic base. Following the addition of LiHMDS, 2.1 equivalents of *s*-BuLi were added, the first to deprotonate hexamethyldisilylazane and the remaining 1.1 equivalents to afford the desired lithiation. Again, no deuteration was observed and only 38% non-deuterated **684** was recovered. Following these unsuccessful results, it was decided move away from isoureas and test other groups as directing groups in lithiation–borylation reactions.

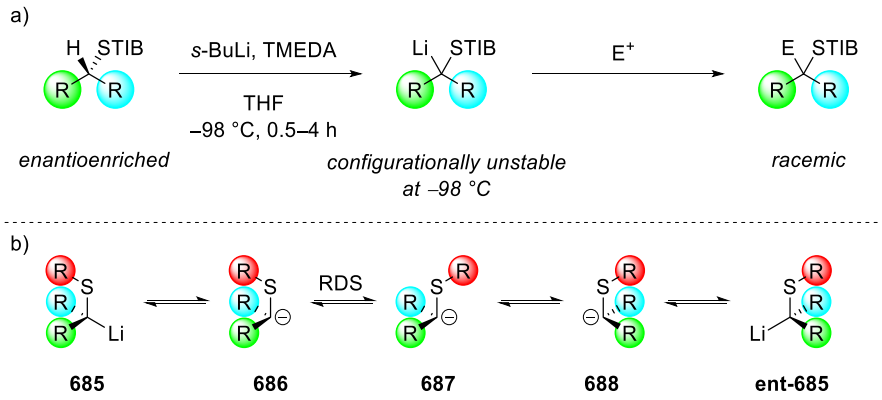


Entry	*s*-BuLi eq	LiHMDS eq	TMEDA eq	D incorp. / %	Recovered SM / %
1	2.1	0	2.1	0	41
2	2.1	1.0	3.1	0	38

Table 19 Attempted lithiation of isourea **684**

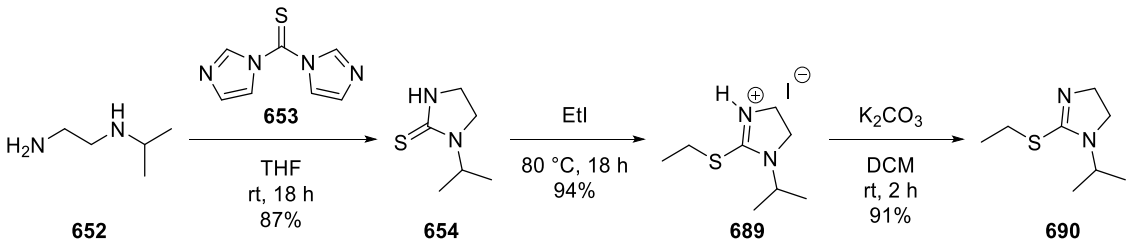
Isothioureas as a leaving group in lithiation–borylation reactions

As with benzoates, α-lithiation of thioesters followed by trapping of the resulting anion with electrophiles is known.[186] In contrast to benzoates,[187] the carbenoids formed are configurationally unstable at –98 °C in THF (Scheme 146a). The reason for this lack of configurational stability is that α–heterosubstituted alkyllithium compounds (where the heteroatom is S, Se, P or Si) undergo a three-step racemisation process (Scheme 146b).[188] Dissociation of the lithium ion of **685** forms contact ion pair **686**. Hyperconjugation of the negative charge into the σ* orbital of the S–R bond stabilises the configuration where the negative charge and sulfur atom bound R group are anti-periplanar to one another; however, when the steric repulsion between R groups is great, a rate-determining rotation of the C–S bond affords configuration **687**. Inversion of the stereocentre restores the stabilising hyperconjugation effect, before reassociation of the lithium ion affords the enantiomer of the original lithiated species **ent-685**. This phenomenon is solvent dependent and it has been shown within our group that by using TBME as solvent and by reducing the lithiation time to five minutes, full deuteration of secondary alkyl STIB compounds can be achieved with an *er* value of 97:3.[189]



Scheme 146 The configurational instability of lithiated thioesters

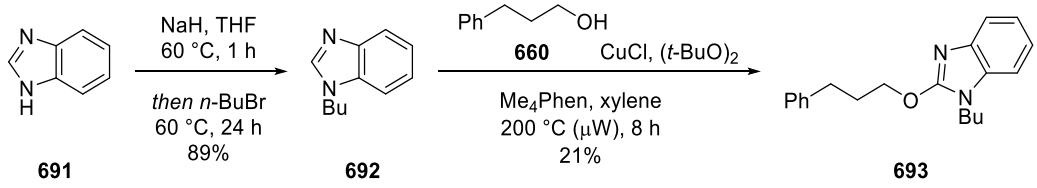
Due to the predicted ease of synthesis we sought to access isothiourea **690** and subject it to lithiation reactions (Scheme 147). Treatment of thioureas **645** with iodoethane at reflux afforded ethyl isothiouroniums **689** in near quantitative yield. Deprotonation with K_2CO_3 then furnished the desired isothiourea **690**. Unfortunately, **690** was insoluble in Et_2O, CPME, TBME, toluene and THF. Attempts were made to lithiate **690** as a suspension; however, these efforts were not fruitful.



Scheme 147 Synthesis of isothiourea **690**

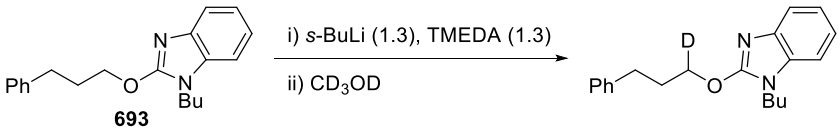
Benzimidazoles as a leaving group in lithiation–borylation reactions

We next sought to use benzimidazole as a directing group in asymmetric lithiation reactions. It was predicted that aromaticity would disfavour direct attack of *s*-BuLi and so prevent decomposition of the substrate through elimination of an alcohol. Due to concerns about poor solubility, *n*-butyl was chosen as the bulky *N*-alkyl group. The synthesis of benzimidazole derivate **693** was achieved in 2 steps (Scheme 148). Benzimidazole (**691**) was first alkylated with *n*-butyl bromide in high yield to afford derivatised benzimidazole **692**. A copper-catalysed coupling, modified from the procedure reported by Kanai,[190] then yielded the desired 2-alkoxy benzimidazole (**693**).



Scheme 148 Synthesis of benzimidazole derivate **693**

2-alkoxy benzimidazole **693** was then subjected to a lithiation–deuteration study (Table 20). Treatment of 2-alkoxyl benzimidazole **693** with 1.3 equiv of *s*-BuLi and 1.3 equiv of TMEDA in Et_2O at −78 °C for 5 h followed by the addition of CD_3OD did not lead to deuteration (Table 20, entry 1). However, we were encouraged that elimination of alcohol **660** was not observed. The lack of deuteration was overcome by increasing the temperature of the lithiation. Treatment of 2-alkoxyl benzimidazole **693** with s-BuLi at –60 °C or –40 °C resulted in complete deuteration after quenching with CD_3OD as determined by ^{1}H NMR analysis, with no deuterium incorporation at the benzylic position (Table 20, entries 2 and 3).



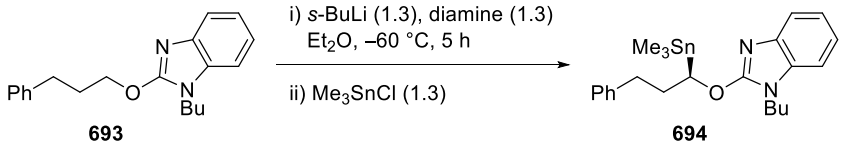
693

Entry	t / h	T / °C	D incorp. / %
1	5	–78 °C	0
2	5	–60 °C	100
3	5	–40 °C	100

Table 20 Lithiation–deuteration studies of 2-alkoxy benzimidazole **693**

With this result in hand we next sought to investigate whether this lithiation could be rendered asymmetric by addition of (+)-sparteine. 2-alkoxy benzimidazole **693** was treated with *s*-BuLi and (+)-sparteine at –60 °C and the resulting lithiated species trapped with trimethyltin chloride to afford stannane **694** (Table 21). Quenching of the lithiated species with Me_3SnCl afforded the expected stannane **694** in good yield when using either TMEDA or (+)-sparteine. Disappointingly, the *ee* value when lithiation was performed in the presence of (+)-sparteine was just 6% (Table 21, entry 2). Poor selectivity in asymmetric lithiation reactions can be caused by a number of factors, such as configurational instability of the lithiated species, reversible trapping of the electrophile or if the electrophile is attacked with a mixture of retention and inversion of the sensitive organolithium. Of these, it seems unlikely that reversible trapping is occurring as Me_3SnCl is not known to trap reversibly with lithiated benzoates.[187] Trapping with mixtures of retention and inversion are generally observed with benzylic substrates,[191] as the lithium carbenoid adopts a partially flattened configuration owing to resonance with the aryl group, with significant electron density opposite the metal. It is therefore also unlikely that this is the cause of the low enantioselectivity. It is known that changing the nature of the directing group directly affects configurational stability of the resulting lithiated species.[186] It is plausible that an aromatic directing group results in the formation of a configurationally labile lithiated species. If this is the case, it might be overcome by employing bisoxazoline ligands, which have been shown to permit homologation of configurationally labile primary benzylic carbamates[186,187] and benzoates[194] in high *ee*. The success of bisoxazolines in the asymmetric lithiation of primary benzylic carbamates and benzoates is because bisoxazolines induce chirality in a thermodynamic manner, ie although the initial selectivity of the deprotonation may be low, the enantiomers are in an equilibrium that favours one enantiomer. It is also plausible that (+)-sparteine ligated *s*-BuLi does not deprotonate with high enantioselectivity, perhaps because it binds to

substrate **693** in a different way from how it binds to benzoate/carbamate substrates. Additionally, it might be that (+)-sparteine is not involved in the lithiation, which could arise from a molecule (or molecules) of substrate **693** disaggregating *s*-BuLi. Due to these unfavourable results, **693** was discarded as a target.



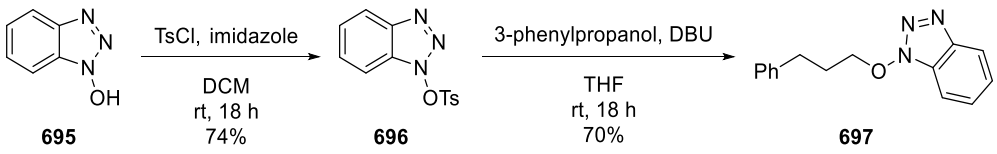
693 **694**

Entry	Diamine	Yield / %	*ee* / %
1	TMEDA	61	0
2	(+)-sp	45	6

Table 21 Synthesis of stannane **694**

Benzotriazole derivatives as a leaving group in lithiation–borylation reactions

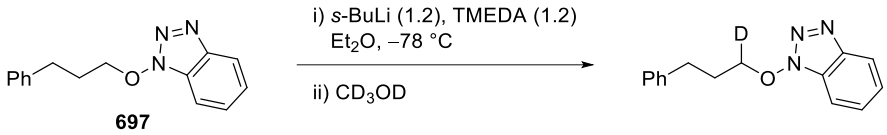
Katritzky has shown that benzotriazole can stabilise α-carbanions generated by lithiation with organolithiums.[195] In light of this interesting reactivity, we next sought to utilize benzotriazole as a directing group in lithiation–borylation reactions. Synthesis of benzotriazole derivative **697** was achieved in a two-step process from HOBt (**695**) (Scheme 149). Treatment of HOBt (**695**) with TsCl and imidazole in DCM afforded tosyl compound **696** in reasonable yield.[196] Simply stirring **696** with 3-phenylpropanol in the presence of DBU afforded benzotriazole derivative **697** in 70% yield.[197] The lithiation of **697** was then evaluated in a lithiation–deuteration study (Table *22*).



695 **696** **697**

Scheme 149 Synthesis of HOBt derivative **697**

Treatment of benzotriazole derivative **697** with 1.2 equiv of *s*-BuLi and 1.2 equiv of TMEDA at −78 °C did not afford deuteration when left for 1, 2 or 3 hours (Table 22, entries 1–3). In addition to this, the levels of recovered starting material were poor, and 3-phenylpropanol (**660**) was detected by TLC analysis in each case. Due to the observed elimination of **660**, it was unlikely that successful lithiation conditions would be found for compound **697** and so this target was abandoned.



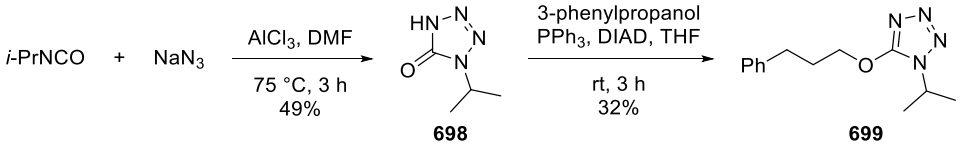
697

Entry	t / h	D incorp. / %	recovered SM / %
1	1	0	65
2	2	0	50
3	3	0	30

Table 22 Lithiation–deuteration studies of benzotriazole derivative **697**

Alkoxytetrazole derivatives as a leaving group in lithiation–borylation reactions

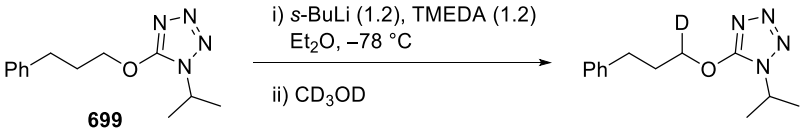
We next turned our attention to the use of tetrazoles. Tetrazole derivative **699** was synthesised in 2 steps isopropyl isocyanate (Scheme 150). $AlCl_3$-assisted cycloaddition of isopropyl isocyanate and sodium azide afforded tetrazolone **698** in moderate yield. Mitsunobu reaction of **698** and 3-phenylpropanol in the presence of DIAD and PPh_3 afforded desired tetrazole derivative **699**, which was subjected to a lithiation study.



698 **699**

Scheme 150 Synthesis of tetrazole derivative **699**

Treatment of tetrazole derivative **699** with 1.2 equiv of *s*BuLi and 1.2 equiv of TMEDA in Et_2O at −78 °C did not afford deuteration incorporation with lithiation times of 1, 2 or 3 h (Table 23, entries 1–3). However, 3-phenylpropanol was not detected by TLC analysis, and the level of starting material recovery was excellent. It is possible that the deuterium incorporation could be increased by optimising the lithiation conditions; however, this work is yet to be performed.



Entry	t / h	D incorp. / %	recovered SM
1	1	0	97
2	2	0	95
3	3	0	87

Table 23 Lithiation–deuteration studies of tetrazole **699**

Conclusion

A new leaving group has been sought to expand the scope of lithiation–borylation reactions to include electron-withdrawing groups, with a specific interest in perfluorinated alkyl groups. Several candidate groups have been investigated, including isoureas, isothioureas, benzimidazoles, benzotriazoles and tetrazoles; however, no satisfactory results were obtained. The most common contraindications were poor levels of lithiation or instability in the presence of *s*-BuLi that resulted in decomposition through the elimination of an alcohol. A notable exception was benzimidazole **693**, which underwent lithiation in the presence of *s*-BuLi and a diamine to afford a chemically stable carbenoid that could be quenched with deuterium or tin electrophiles; however, this reaction could not be made enantioselective through the utilization of (+)-sparteine. The most likely cause of the poor enantioselectivity values obtained when quenching with tin electrophiles is that the generated carbenoid is configurationally labile. Utilization of a ligand that infers chirality through a thermodynamic deprotonation, such as a bisoxazoline, may permit the generation of an enantiopure carbenoid that can be quenched with electrophiles with a high *ee* value.

General Conclusion

This thesis has served to document the contributions made to four projects, three of which focussed on the synthesis and reactivity of 1,2-bis(boronic esters) and the fourth concentrated on expanding the scope of the lithiation–borylation reaction.

In the first project, the synthesis of the atorvastatin derivative, **223**, was achieved by combining Morken's asymmetric diboration reaction with the Aggarwal group's lithiation–borylation methodology. This method of generating 1,3-bis(boronic esters) proved to be superior to reactions of lithiated carbamates/benzoates with diborylmethane because benzoate **294** was resistant to deprotonation.

The total synthesis of bahamaolide A was then undertaken using an iterative diboration–homologation sequence to construct the polyol portion of the natural product. This synthesis aimed to champion the boronic ester moiety as a functional group handle by masking eight of the nine stereodefined hydroxyl groups as boronic esters, which were revealed simultaneously through stereospecific oxidation of the carbon–boron bonds. The greatest challenge of this project was the purification of poly(boronic ester) intermediates, which inhibited the process of carrying material through the synthetic sequence. Nevertheless, after optimisation of these bottlenecks we were able to acquire a crude sample of the presumed natural product, which is currently awaiting purification by reverse phase prepHPLC.

The third project was concerned with the development of a novel boronic ester protecting group to allow the selective homologation of a 1,2-bis(boronic ester) through the more hindered internal boron moiety. Aminodiols **590**, **591** and **593** were identified as suitable candidates, and each displayed ^{11}B NMR chemical shift values, once coordinated to a simple boronic acid, that confirmed that all three lowered the Lewis acidity of the boron centre relative to a pinacol boronic ester. Disappointingly, boronic esters **594**, **595** and **597** interacted unfavourably with silica gel and so **590**, **591** and **593** were discarded as targets. Diamine **609** showed an improved stability profile when coordinated to a simple boronic acid, and was shown to be a suitable protecting group in the homologation of boronic esters with magnesium carbenoids derived from the corresponding α–sulfinyl benzoates. The synthesis of mixed diboron species **615** was synthesised in low yield and has been shown to be a suitable reagent for the synthesis of primary protected 1,2-bis(boronic esters).

Finally, a new leaving group to be used in lithiation–borylation reactions has been sought. A number of functional groups were investigated, such as isoureas, isothioureas, benzimidazoles, tetrazoles and benzotriazoles; however, a suitable group was not identified.

Experimental section

General experimental

Solvents and reagents

All air- and water-sensitive reactions were carried out in flame-dried glassware under a nitrogen or argon atmosphere using standard Schlenk manifold technique. Anhydrous solvents were commercially supplied or provided and dried using a purification column composed of activated alumina and stored over thoroughly dried 3 Å molecular sieves by the communal stills of the School of Chemistry, University of Bristol.[198]

n-Butyl lithium [CAS: 109-72-8] was purchased from Acros (181271000) as a 1.60 M solution in *n*-hexane. *s*-Butyl lithium [CAS: 598-30-1] was purchased from Acros (187541000) as a 1.30 M solution in cyclohexane:*n*-hexane 98:2. *t*-Butyl lithium [CAS: 594-19-4] was purchased from Sigma-Aldrich (186198) as a 1.70 M solution in *n*-pentane. (+)-Sparteine and (−)-sparteine were obtained from the commercially available sulphate pentahydrate salt (99%, Acros) and isolated according to literature procedure.[199] The sparteine free base readily absorbs atmospheric carbon dioxide (CO_2) and so should be stored under argon/nitrogen at −20 °C in a sealed Schlenk-tube. The molarity of organolithium solutions was regularly determined by titration using *N*-benzyl benzamide as an indicator.[200]

All other reagents were purchased from various commercial sources and used as received or synthesised according to the procedures given.

Chromatography, Spectroscopy and Apparatus

Flash column chromatography (FCC) was carried out using Fluorochem silica gel LC60A-40 (63 μm) or Aldrich technical grade silica gel (40-63 μm). All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F254 fluorescent treated silica which was visualized under UV light or by staining with aqueous basic potassium permanganate.

^{1}H, ^{13}C and **^{11}B NMR** spectra were recorded using Jeol ECP(Eclipse) 300 MHz, Jeol ECS 400 MHz, Bruker 400 MHz, Varian VNMR 400 MHz, Varian VNMR 500 MHz, and Bruker Advance III HD 500 MHz cryo spectrometers. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz), rounded to the nearest 0.5 Hz. The ^{1}H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons, assignment). NMR assignments are made

according to spin systems, using two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy to assist the assignment. Where an assignment could not be made unambiguously, possible assignments are listed.

High resolution mass spectra (**HRMS**) were recorded on a VG Analytical Autospec by Electron Ionization (EI) or Chemical Ionization (CI), or on a Bruker Daltonics Apex IV or Bruker micrOTOF II by Electrospray Ionization (ESI), or on a Bruker Daltonics UltrafleXtreme (MALDI).

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film. Only selected absorption maxima (νmax) are reported in wavenumbers (cm–1).

Melting points were recorded in degrees Celsius (°C), using a Kofler hot-stage microscope apparatus and are reported uncorrected.

Optical rotation ($[\alpha]_D^T$) was measured on a Bellingham and Stanley Ltd. ADP220 polarimeter and is quoted in (° ml)(g dm)$^{-1}$.

Chiral HPLC was performed on a HP Agilent 1100 with a Chiralpak IA, IB or IC column, or a Chiralcel AD-H column, and monitored by DAD (Diode Array Detector).

Chiral GC was performed on an Agilent 7890A using Chiraldex □-DP 120 (30m x 0.25mm x 0.25μm).

Chiral SFC was performed on a Waters TharSFC system using a Diacel Chiralpak IB column (4.6 m × 250 mm × 5 μm) and monitored by DAD (Diode Array Detector).

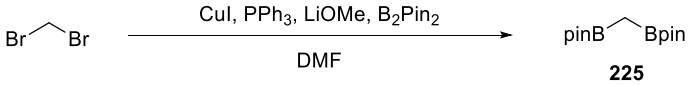
GC-MS was performed on an Agilent 7820A using a HP-5MS UI column (30 m × 0.25 mm × 0.25 μm).

Naming of Compounds

Compound names are those generated by ChemBioDraw 13.0/14.0 software (PerkinElmer), following the IUPAC nomenclature.

Experimental procedures and characterisation data

Bis(4, 4, 5, 5,-tetramethyl-1, 3, 2-dioxaborolan-2-yl)methane **(225)**



225

According to a modified literature procedure,[201] Copper(I) iodide (1.87 g, 0.0098 mmol, 1.0 mol%), triphenylphosphine (3.40 g, 0.013 mmol), lithium methoxide (11.2 g, 0.294 mmol, 3.0 equiv) and bis(pinacolato)diboron (50.0 g, 0.197 mmol, 2.0 equiv)) were charged to a flame-dried three-neck flask under an atmosphere of nitrogen. Dibromomethane (6.90 ml, 0.098 mmol, 1.0 equiv) in anhydrous DMF (197 ml,) was added at 0 °C resulting in a black solution. The reaction mixture was warmed to ambient temperature and stirred for 16 h. The reaction mixture was then diluted with Et_2O (50 ml) and filtered through a Celite plug. The mother liquor was washed with water (3 x 50 ml), brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a colourless oil, which solidified under high vacuum to afford **225** (13.8 g, 52%) as an amorphous white solid.

Spectral data in accordance with the published values[201]

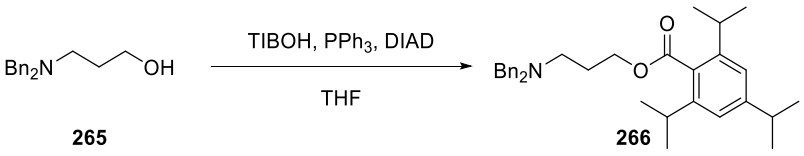
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (m, 24H, 8 x CH_3), 0.33 (s, 2H, BCH_2B) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 83.0 (C), 24.7 (CH_3) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

^{11}B NMR (96 MHz) δ 32.4 (s) ppm.

3-(Dibenzylamino)propyl 2,4,6-triisopropylbenzoate (**266**)



265 **266**

According to a modified literature procedure,[185] diisopropyldiazodicarboxylate (4.25 ml, 21.6 mmol, 1.10 equiv) was added dropwise to a stirred solution of 3-(dibenzylamino)propan-1-ol (**265**) (5.00 g, 19.6 mmol, 1.00 equiv), triisopropylbenzoic acid (5.59 g, 22.5 mmol, 1.15 equiv) and triphenylphosphine (5.64 g, 21.6 mmol, 1.10 equiv). in anhydrous THF (0.66 M, 30.0 ml) at 0 °C under a nitrogen atmosphere. Upon

completion of the addition the reaction mixture appeared pale yellow. The reaction mixture was warmed to ambient temperature and stirred for 16 h. At this point the reaction mixture was concentrated *in vacuo* to a yellow oil. This oil was triturated in pentane, causing the precipitation triphenylphosphine oxide. The triphenylphosphine oxide was filtered, and the mother liquor concentrated *in vacuo* to a yellow oil. The crude residue was purified by column chromatography (SiO_2, pentane:Et_2O 95:5) to yield the title compound (**266**) (8.30 g, 87%) as an amorphous white solid.

R_f 0.34 (pentane/Et_2O, 90:10)

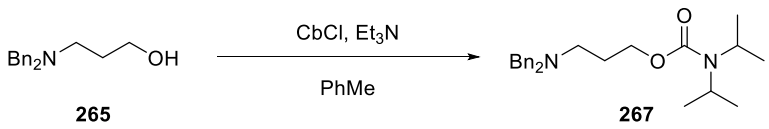
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 4H, Ar*H*), 7.29 (m, 4H, Ar*H*), 7.21 (m, 2H, Ar*H*), 6.98 (s, 2H, Ar*H*), 4.32 (t, J = 6.8 Hz, 2H, OCH_2), 3.57 (s, 4H, N(CH_2Ph)$_2$), 2.88 (sept, J = 6.9 Hz, 1H, *para*-C*H*), 2.80 (sept, J=6.8 Hz, 2H, 2 x *ortho*-C*H*), 2.57 (t, J = 6.8, 2H, NCH_2), 1.92 (p, J = 6.8, 2H, NCH$_2$CH_2), 1.24 (d, J = 6.9 Hz, 6H, *para*-CH(CH_3)$_2$), 1.20 (d, J = 6.8 Hz, 12H, 2 x *ortho*-CH(CH_3)$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.2 (C), 144.9 (C), 139.6 (C), 130.7 (C), 128.9 (CH), 128.4 (CH), 127.0 (CH), 121.0 (CH), 63.7 (CH_2), 58.5 (CH_2), 50.8 (CH_2), 34.6 (CH), 31.6 (CH), 26.7 (CH_2), 24.3 (CH_3), 24.1 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat): 2963.6, 2795.8, 1721.0, 1248.6 and 1081.2.

HRMS (ESI) calculated for $C_{33}H_{44}NO_2$ $[M+H]^+$ 486.3367, found: 486.3357.

3-(Dibenzylamino)propyl diisopropylcarbamate (**267**)



265 **267**

According to a modified literature procedure,[175] triethylamine (1.81 ml, 13.0 mmol, 1.30 equiv) was added to a stirred solution of 3-(dibenzylamino)propan-1-ol (**265**) (2.55 g, 10.0 mmol, 1.00 equiv) and diisopropylcarbamoyl chloride (1.96 g, 12.0 mmol 1.20 equiv) in anhydrous toluene (1.00 M, 10.0 ml). The solution was stirred briefly to ensure complete dissolution before being heated at 150 °C for 2 h under microwave irradiation. The reaction mixture was filtered through a plug of silica gel eluting with Et_2O and

concentrated to a yellow oil. This oil was purified by bulb-to-bulb distillation to yield the title compound (**267**) (3.10 g, 81%) as a yellow oil.

R_f 0.42 (DCM)

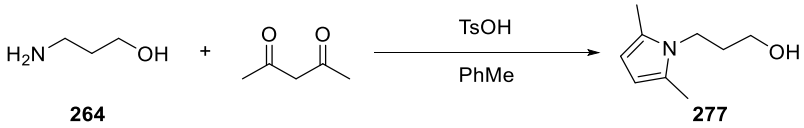
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 4H, Ar*H*), 7.29 (t, J = 7.4, 4H, Ar*H*), 7.23–7.19 (m, 2H, Ar*H*), 4.10 (t, J = 6.3, 2H, OCH_2), 3.56 (s, 4H, N(CH_2Ph)$_2$), 2.53 (t, J = 7.1 Hz, 2H, NCH_2), 1.85 (p, J = 6.3 Hz, NCH$_2$CH_2), 1.10 (br. s, 12H, N(CH(CH_3)$_2$)$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (C=O), 139.7 (C), 128.7 (CH), 128.2 (CH), 126.8 (CH), 62.9 (CH_2), 58.4 (CH_2), 50.3 (CH_2), 45.4 (CH), 26.8 (CH_2), 20.8 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat): 2965.4, 2796.7, 1687.1, 1451.2 and 1288.8.

HRMS (ESI) calculated for $C_{24}H_{35}N_2O_2$ $[M+H]^+$ 383.2693, found: 383.2681.

1-(3-Hydroxypropyl)-2,5-dimethylpyrrole (**277**)



264 **277**

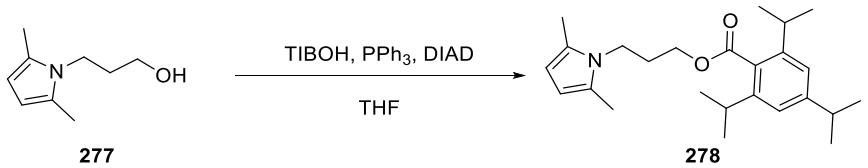
According to a literature procedure,[202] *p*-toluenesulfonic acid (138 mg, 0.80 mmol, 20.0 mol%) was added to a stirred solution of 3-amino-1-propanol (**264**) (3.05 ml, 39.9 mmol, 1.00 equiv) and acetonylacetone (5.60 ml, 47.9 mmol, 1.20 equiv) in toluene (0.11 M, 362 ml) and the resulting solution was heated at reflux with a Dean−Stark trap for 16 h. After this time, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to a deep red oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 20:80) to yield **277** (6.04 g, 99%) as a red oil.

All data matched that reported in the literature.[203]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (br. s, 2H, Ar*H*), 3.89 (m, 2H, OCH_2), 3.69 (t, J = 6.0 Hz, 2H, NCH_2), 2.24 (s, 6H, 2 x NC(CH_3)$_2$), 1.87 (m, 2H, NCH$_2$CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 127.6 (C), 105.2 (CH), 60.2 (CH_2), 40.5 (CH_2), 33.7 (CH_2), 12.6 (CH_3) ppm.

3-(2,5-Dimethyl-1*H*-pyrrol-1-yl)propyl-2,4,6-triisopropylbenzoate (**278**)



277 **278**

According to a modified literature procedure,[185] diisopropylazodicarboxylate (2.06 ml, 10.8 mmol, 1.10 equiv) was added dropwise to a stirred solution of triphenylphosphine (2.82 g, 10.77 mmol, 1.10 equiv), 3-(2,5-dimethyl-1*H*-pyrrol-1-yl)propan-1-ol (**277**) (1.50 g, 9.79 mmol, 1.00 equiv) and 2,4,6-triisopropylbenzoic acid (2.80 g, 11.26 mmol, 1.15 equiv) in dry THF (0.66 M, 14.8 mmol) at 0 °C over 10 min. The resulting reaction mixture was warmed to ambient temperature and stirred at this temperature for 16 h. The reaction mixture was then concentrated *in vacuo* to a yellow oil. This oil was triturated in pentane, filtered and concentrated to another yellow oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 90:10) to afford the title compound (**278**) (3.30 g, 89%) as a colourless oil which later solidified to an amorphous white solid.

***R*f** 0.3 (pentane/Et_2O, 90:10)

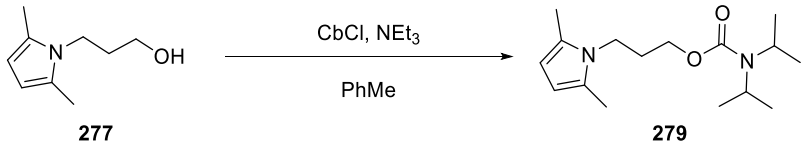
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H, Ar*H*), 5.78 (br. s, 2H, Ar*H*), 4.35 (t, *J* = 6.2 Hz, 2H, OCH_2), 3.88 (m, 2H, NCH_2), 2.90 (hept, *J* = 6.8 Hz, 1H, *para*-C*H*), 2.84 (sep, *J* = 6.8 Hz, 2H, 2 x *ortho*-C*H*), 2.22 (s, 6H, N(CCH_3)$_2$), 2.09–2.02 (m, 2H, NCH$_2$CH_2), 1.26 (d, *J* = 7.2 Hz, 18H, 3 x CH(CH_3)$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C=O), 150.4 (C), 144.9 (C), 130.3 (C), 127.4 (C), 121.0 (CH), 105.5 (CH), 62.4 (CH_2), 40.8 (CH_2), 34.5 (CH), 31.7 (CH), 30.3 (CH_2), 24.3 (CH_3), 24.0 (CH_3), 12.6 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat): 2958.0, 1720.3, 1251.6, 1072.6 and 750.1.

HRMS (ESI) calculated for $C_{25}H_{38}NO_2$ $[M+H]^+$ 384.2897, found: 384.2912.

3-(2,5-Dimethyl-1*H*-pyrrol-1-yl)propyl diisopropylcarbamate (**279**)



According to a modified literature procedure,[175] triethylamine (1.77 ml, 12.7 mmol, 1.30 equiv) was added to a stirred solution of 3-(2,5-dimethyl-1*H*-pyrrol-1-yl)propan-1-ol (**277)** (1.5 g, 9.8 mmol, 1.00 equiv) and diisopropylcarbamoyl chloride (1.91 g, 11.7 mmol, 1.20 equiv) in anhydrous toluene (1.00 M, 9.80 ml). The resulting reaction mixture was heated at 150 °C in a sealed tube for 2 h under microwave irradiation. The reaction mixture was cooled to ambient temperature, filtered through a plug of silica gel eluting with Et_2O and concentrated to a brown oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 80:20) to yield **279** (2.18 g, 79%) as a colourless oil.

***R*f** 0.08 (pentane/Et_2O, 90:10)

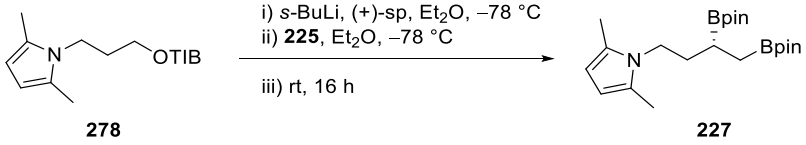
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (br. s, 2H, Ar*H*), 4.14 (t, *J* = 6.0 Hz, 2H, OCH_2), 3.90 (br. s, 2H, N(C*H*)$_2$), 3.87–3.83 (m, 2H, NCH_2), 2.22 (s, 6H, NC(CH_3)$_2$), 1.97 (m, 2H, NCH$_2$CH_2), 1.23 (d, *J* = 6.8 Hz, 12H, 2 x NCH(CH_3)$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C=O), 127.4 (C), 105.4 (CH), 62.0 (CH_2), 46.1 (CH), 41.0 (CH_2), 30.7 (CH_2), 21.1 (CH_3), 12.5 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat): 2968.4, 1688.1, 1288.0, 1063.8 and 746.4.

HRMS (ESI) calculated for $C_{16}H_{29}N_2O_2$ $[M+H]^+$ 281.2224, found: 281.2223.

(*R*)-1-(3,4-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-2,5-dimethyl-1H-pyrrole (**227**)



s-BuLi (1.30 M in hexanes, 3.60 ml, 4.70 mmol, 1.20 equiv) was added dropwise to a stirred solution of 3-(2,5-dimethyl-1*H*-pyrrol-1-yl)propyl-2,4,6-triisopropylbenzoate (**278**) (1.50 g, 3.91 mmol, 1.00 equiv) and (+)-sparteine (1.08 ml, 4.70 mmol, 1.20 equiv)

in anhydrous Et_2O (0.33 M, 11.8 ml) at −78 °C under an atmosphere of nitrogen. The resulting mixture was stirred at –78 °C for 3 h. A solution of diborylmethane (**225**) (1.57 g, 5.97 mmol, 1.50 equiv) in anhydrous Et_2O (0.50 M, 11.9 ml) was added dropwise and stirred for 1 h at −78 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 h before being diluted with water (50 ml) and Et_2O (50 ml). The layers were separated, and the aqueous phase extracted with Et_2O (3 x 50 ml), washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to an orange oil. This residue was purified by column chromatography (SiO_2, pentane:Et_2O 90:10) to afford the title compound (**227**) (0.99 g, 63%, 97:3 *er*) as a colourless oil.

$\boldsymbol{R_f}$ 0.17 (pentane/Et_2O, 90:10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07–4.67 (br. s, 2H, Ar*H*), 3.80–3.63 (m, 2H, NCH_2), 2.20 (s, 6H, N(CCH_3)$_2$), 1.70 (m, 1H, NCHCH_aH$_b$), 1.60 (m, 1H, NCHCH$_a$$H_b$), 1.27–1.18 (m, 24H, 8 x pinacol-CH_3), 1.23 (m, 1H, BC*H*), 0.96 (dd, *J* = 15.8, 8.9 Hz, 1H, BCH_aH$_b$), 0.85 (dd, *J* = 15.8, 6.2 Hz, 1 H, BCH$_a$$H_b$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 127.4 (C), 104.8 (CH), 83.2 (pinacol-C), 83.1 (pinacol-C), 43.4 (CH_2), 34.8 (CH_2), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 12.4 (CH_3) ppm.

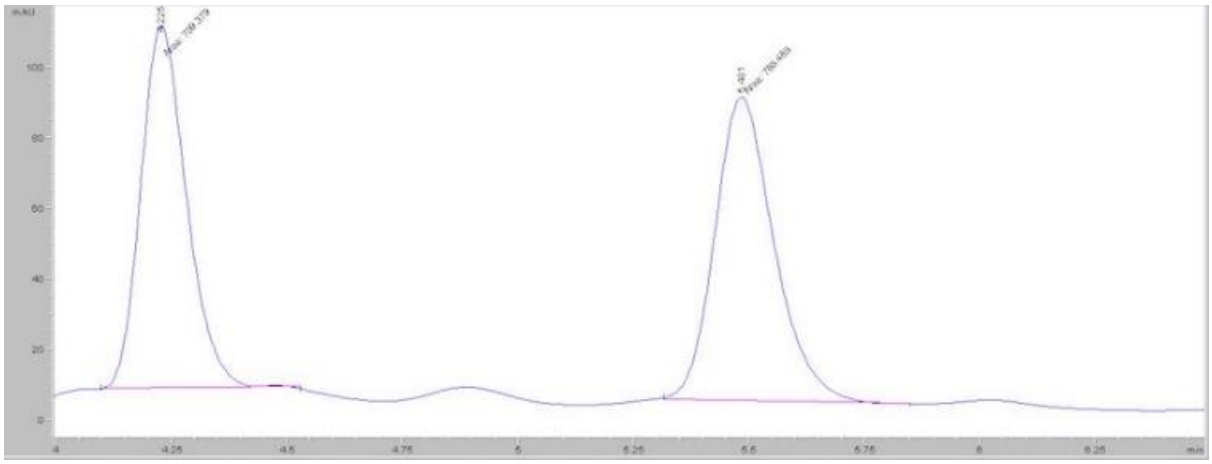
Carbon atoms next to boron not observed due to quadrupolar relaxation

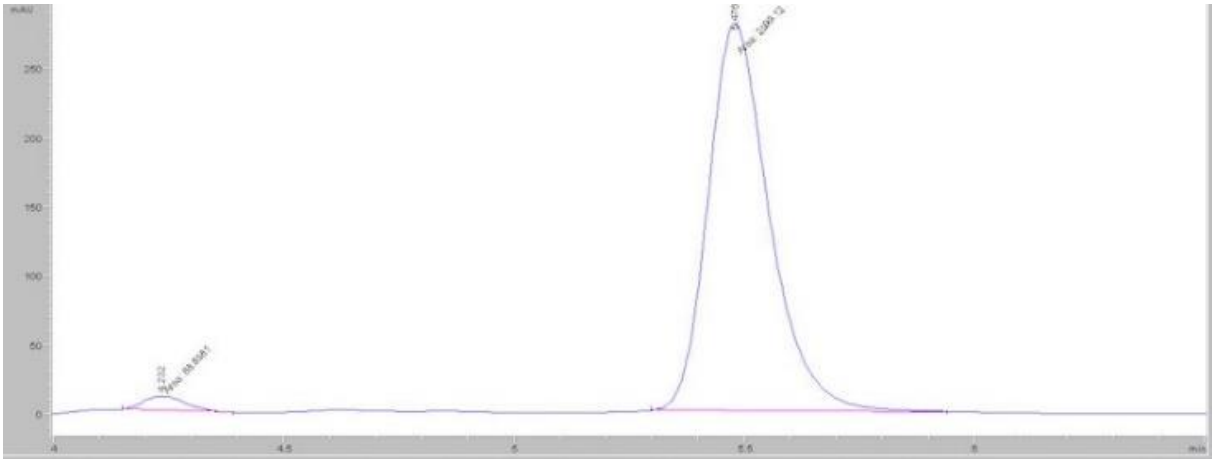
IR (ν_{max}/cm^{-1}, neat): 2976.40, 1369.0, 1140.4, 967.6, 845.2 and 743.7.

HRMS (ESI) calculated for $C_{22}H_{40}B_2NO_4$ $[M+H]^+$ 404.3138, found: 404.3140.

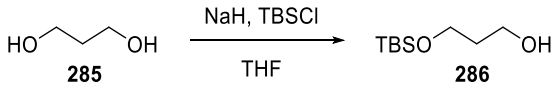
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{22}}$**(**$CHCl_3$, *c* = 1) +1.

Chiral HPLC: (Diacel Chiralpak IB column (25 cm) with guard, hexane:IPA (1:1), 1.0 ml/min, room temperature, 210 nm): t_R = 4.23 min (minor), 5.48 min (major), *er* = 97:3.





3-((*t*-Butyldimethylsilyl)oxy)propan-1-ol (**286**)



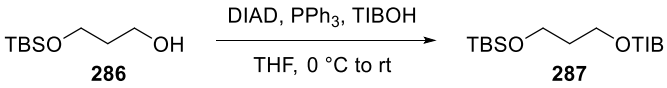
According to a modified literature procedure,[202] 1,3-propanediol (**285**) (9.50 ml, 126.4 mmol, 1.00 equiv) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 5.06 g, 126 mmol. 1.00 equiv) in anhydrous THF (0.20 M, 632 ml) at 0 °C under an atmosphere of nitrogen. The resulting mixture was warmed to ambient temperature and stirred for 1 h. The reaction mixture was then cooled to 0 °C and TBSCl (19.1 g, 126 mmol, 1.00 equiv) was added portion wise. The resulting mixture was warmed to ambient temperature and stirred for 1 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (250 ml) and was diluted with Et_2O (100 ml). The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 100 ml). The combined organics were washed with brine (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **286** (23.5 g, 98%) as a colourless oil.

All data matched that reported in the literature.[202]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (m, 2H, OCH_2), 3.80 (m, 2H, OCH_2), 2.54 (br. s, 1H, O*H*), 1.78 (m, 2H, OCH_2CH_2), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 6H, Si(CH_3)$_2$). ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 62.9 (CH_2), 62.4 (CH_2), 34.2 (CH_2), 25.9 (C), 18.2 (CH_3), –5.5 (CH_3) ppm.

3-((*t*-Butyldimethylsilyl)oxy)propyl 2,4,6-triisopropylbenzoate (**287**)



Diisopropyl azodicarboxylate (0.10 ml, 0.52 mmol, 1.10 equiv) was added dropwise to a solution of 3-((*t*-butyldimethylsilyl)oxy)propan-1-ol (**286**) (89.5 mg, 0.47 mmol, 1.00 equiv), triphenyl phosphine (136 mg, 0.52 mmol, 1.10 equiv) and 2,4,6-triisopropylbenzoic acid (134 mg, 0.54 mmol, 1.15 equiv) in anhydrous THF (0.66 M, 0.71 ml) at 0 °C. The resulting solution was warmed to ambient temperature and was stirred at this temperature for 4 h. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane:Et_2O 99:1) to yield **287** (135 mg, 68%) as a colourless oil.

$\boldsymbol{R_f}$ 0.62 (pentane:Et_2O 97:3)

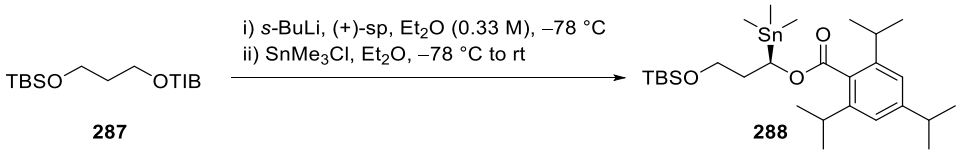
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, Ar*H*), 4.40 (t, *J* = 6.4 Hz, 2H, TIBOCH_2), 3.72 (t, *J* = 6.1, SiOCH_2), 2.89 (hept, *J* = 6.9 Hz, 1H, *para*-C*H*(CH_3)$_2$), 2.85 (sept, *J* = 6.9 Hz, 2H, 2 x *ortho*-C*H*(CH_3)$_2$), 1.93 (app p, *J* = 6.4 Hz, 2H, OCH_2CH_2), 1.24 (d, *J* = 6.9 Hz, 18H, 3 x CH(CH_3)$_2$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.1 (C), 144.8 (C), 130.7 (C), 120.9 (CH), 62.1 (CH_2), 59.6 (CH_2), 34.5 (CH), 32.0 (CH_2), 31.6 (CH), 26.0 (CH_3), 24.2 (CH_3), 24.0 (CH_3), 18.3 (C), –5.3 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat) 2958, 2869, 1726, 1462, 1250, 1073 and 836.

HRMS (ESI) calculated for $C_{25}H_{44}NaO_3Si$ $[M+Na]^+$ 443.2952, found 443.2940.

(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-(trimethylstannyl)propyl 2,4,6-triisopropylbenzoate (**288**)



According to a modified literature procedure,[52] a flame dried Schlenk tube was attached to a vacuum manifold. The reaction flask was evacuated and refilled with nitrogen three times. 3-((*t*-Butyldimethylsilyl)oxy)propyl 2,4,6-triisopropylbenzoate (**287**) (1.00 g, 2.38 mmol, 1.00 equiv) and (+)-sparteine (0.71 ml, 3.10 mmol, 1.30 equiv) were added to the vessel followed by the addition of anhydrous Et_2O (0.24 M, 9.70 ml). The solution was cooled to −78 °C and was allowed to equilibrate for 5 min. *s*-BuLi (1.30 M in hexanes, 2.38 ml, 3.10 mmol, 1.30 equiv) was added dropwise over 10 min (colour change: colourless to brown) and the resulting solution was stirred at −78 °C for 4 h. Me_3SnCl (1.00 M in hexanes, 3.10 ml, 3.10 mmol, 1.30 equiv) was then added dropwise over 15 min and the resulting solution was stirred at −78 °C for 20 min (colour change: brown to yellow to white). The reaction mixture was warmed to ambient temperature and stirred for 1 h. The reaction mixture was diluted with an aqueous solution of HCl (2.00 M, 30.0 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 50ml) and was kept for sparteine recovery. The combined ethereal layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated to a colourless oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 96:4) to afford the title compound (**288**) (1.16 g, 84%, 95:5 *er*) as a colourless oil.

$\boldsymbol{R_f}$ 0.33 (pentane:Et_2O, 98:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 2H, Ar*H*), 5.09–5.04 (m, 1H, SnC*H*), 3.72–3.66 (m, 2H, OCH_2), 2.88 (hept, J = 6.8 Hz, 1H, *para*-C*H*), 2.81 (hept, J = 6.8 Hz, 2H, 2 x *ortho*-C*H*), 2.20–1.98 (m, 2H, OCH_2CH_2), 1.25–1.23 (m, 2 x *ortho*-CH(CH_3)$_2$), 1.22–1.19 (m, 6H, *para*-CH(CH_3)$_2$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.19 (s and d, J = 54.1 Hz and d, J = 51.8 Hz, 9 H, (SnCH_3)$_3$), 0.04 (s, 6H, Si(CH_3)$_2$) ppm.

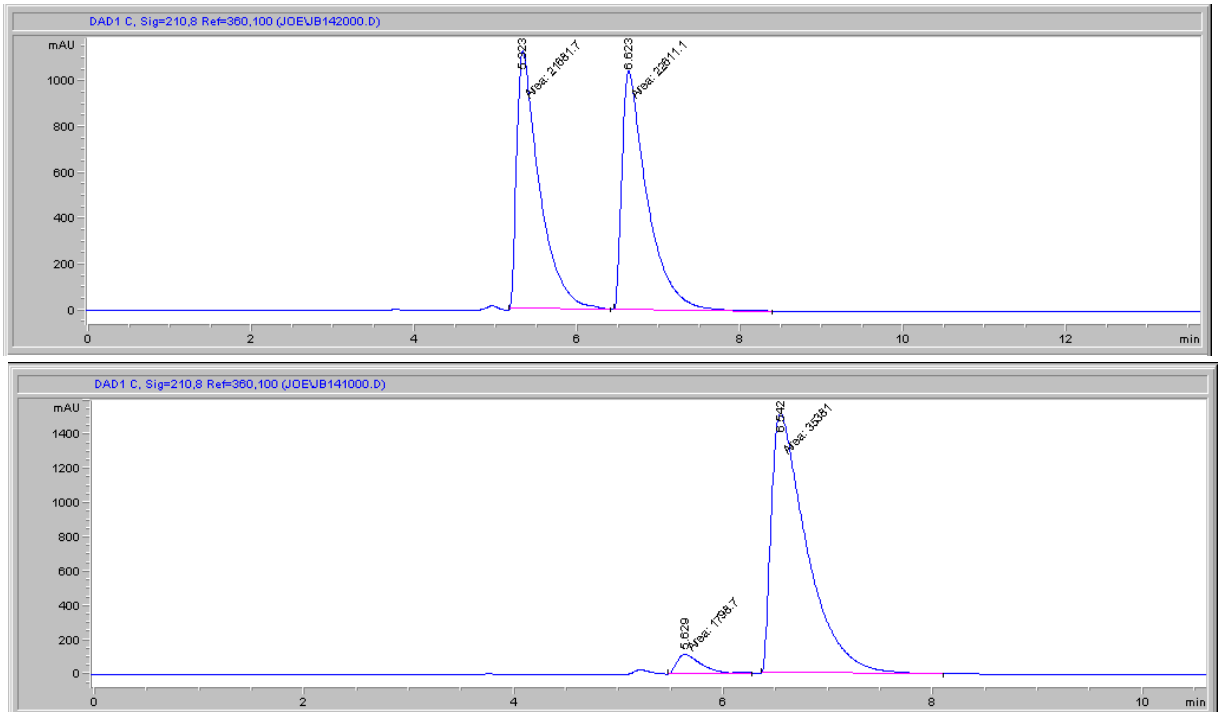
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C=O), 149.9 (C), 144.8 (C), 130.7 (C), 120.8 (CH), 68.5 (CH), 61.0 (CH_2), 36.9 (CH_2), 34.4 (CH), 31.4 (CH), 25.9 (CH_3), 24.3 (CH_3), 23.9 (CH_3), 18.3 (C), –5.3 (CH_3), –8.8 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat): 2958.5, 1707.4, 1461.9, 1250.6, 1069.3 and 773.7.

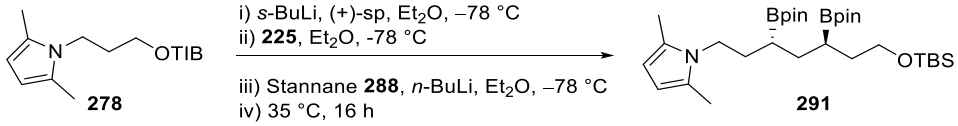
HRMS (ESI) calculated for $C_{28}H_{52}NaO_3SiSn$ $[M+Na]^+$ 607.2600, found: 607.2603.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$(CHCl$_3$, *c* = 1) –34.

Chiral HPLC: (Diacel Chiralpak IB column (25 cm) with guard, hexane, 0.9 ml/min, room temperature, 210 nm): t_R = 5.63 min (minor), 6.54 (major), *er* = 95:5.



1-((3*R*-5*R*)-7-((*t*-Butyldimethylsilyl)oxy)-3,5,-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl)-2,5-dimethyl-1*H*-pyrrole (**291**)



To a stirred solution of 3-(2,5-dimethyl-1*H*-pyrrol-1-yl)propyl-2,4,6-triisopropylbenzoate (**278**) (0.33 g, 0.85 mmol 1.00 equiv) and (+)-sparteine (0.20 ml, 0.85 mmol, 1.00 equiv) in anhydrous Et_2O (0.33 M, 2.60 ml) under a nitrogen atmosphere in the 'A' side of the Aggarwal inverse addition vessel at –78 °C was added *s*-BuLi (1.30 M in hexanes, 0.65 ml, 0.85 mmol, 1.00 equiv) dropwise to give a brown solution. The resulting solution was stirred at –78 °C for 3 h. To a stirred solution of (R)-3-((*t*-butyldimethylsilyl)oxy)-1-(trimethylstannyl)propyl 2,4,6-triisopropylbenzoate (**288**)

(0.93 g, 1.6 mmol, 1.90 equiv) in anhydrous Et_2O (0.33 M, 4.80 ml) in the 'B' side of the Aggarwal inverse addition vessel at –78 °C was added *n*-BuLi (1.60 M in hexanes, 0.95 ml, 1.53 mmol, 1.80 equiv) dropwise at – 78 °C to give a red solution. The resulting solution was stirred at this temperature for 1 h. Concurrently, a solution of diborylmethane (**225**) (0.22 g, 0.85 mmol, 1.00 equiv) in anhydrous Et_2O (0.50 M, 1.70 ml) was added dropwise to the 'A' side of the Aggarwal inverse addition vessel and stirred at –78 °C for 1 h. After this time the carbenoid in side 'B' was tipped portionwise into side 'A' and the resulting solution stirred for a further hour at –78 °C. The reaction was warmed to ambient temperature and then heated at 35 °C for 16 h. The reaction mixture was diluted with water (50 ml) and Et_2O (50 ml). The layers were separated and the aqueous phase extracted with Et_2O (3 x 50ml), washed with brine (50ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to an amber oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 90:10) to yield the title compound (**291**) (115 mg, 24%) as a colourless oil.

$\boldsymbol{R_f}$ 0.26 (pentane/Et_2O, 90:10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07–5.25 (br. s, 2H, Ar*H*), 3.72–3.63 (m, 2H, NCH_2), 3.63–3.52 (m, 2H, OCH_2), 2.22–2.17 (m, 6H, N(CCH_3)$_2$), 1.69–1.55 (m, 2H, NCH$_2$CH_2), 1.69–1.55 (m, 2H, OCH$_2$CH_2), 1.55–1.47 (m, 2H, NCH$_2$CH$_2$C*H* and OCH$_2$CH$_2$C*H*), 1.26–1.18 (m, 24H, 8 x pinacol-CH_3), 1.10–1.00 (m, 2H, BCCH_2CB), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.03 (s, 6H, Si(CH$_3$)$_2$) ppm.

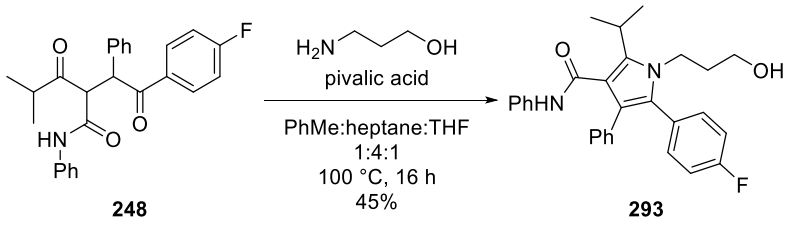
^{13}C NMR (101 MHz, $CDCl_3$) δ 127.0 (C), 104.5 (CH), 83.3 (pinacol-C), 83.1 (pinacol-C), 63.1 (CH$_2$), 43.3 (CH$_2$), 35.1 (CH$_2$), 33.1 (CH$_2$), 32.8 (CH$_2$), 25.0 (pinacol-CH$_3$), 25.0 (pinacol-CH$_3$), 24.7 (CH$_3$), 17.9 (C), 12.1 (CH$_3$), –5.6 (CH$_3$) ppm.

Carbon atoms next to boron not observed due to quadrupolar relaxation.

IR (ν_{max}/cm^{-1}, neat): 2976.2, 2928.3, 2856.8, 1378.3, 1141.7 and 835.0.

HRMS (ESI) calculated for $C_{31}H_{60}B_2NO_5Si$ $[M+H]^+$ 576.4421, found: 576.4422.

5-(4-Fluorophenyl)-1-(3-hydroxypropyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (**293**)



Pivalic acid (0.19 g, 1.81 mmol, 0.20 equiv) was added to a solution of 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide (**248**) (1.02 g, 9.05 mmol, 1.00 equiv) and 3-aminopropan-1-ol (1.04 mL, 13.6 mmol, 1.50 equiv) in a mixture of toluene (4.5 mL), heptane (18.0 mL) and THF (4.5 mL). The reaction mixture was stirred at 120 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and diluted with H_2O (50 mL) and Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, Et_2O:pentane 60:40) to yield **293** (2.67 g, 65%) as a white solid.

***R*f** 0.24 (Et_2O:pentane 60:40)

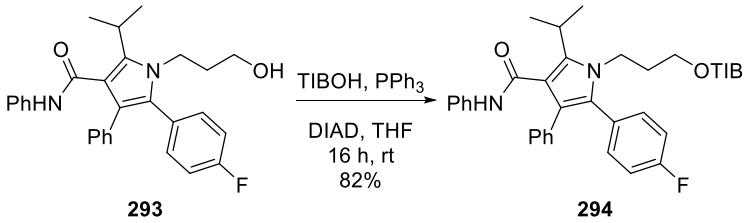
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.15 (m, 9H, Ar*H*), 7.08–7.04 (m, 2H, Ar*H*), 6.95–7.03 (m, 3H, Ar*H*), 6.86 (br. s, 1H, N*H*), 4.03–3.99 (m, 2H, OCH_2), 3.56 (hept, *J* = 7.2 Hz, 1H, C*H*), 3.51 (dd, *J* = 10.9, 5.6 Hz, 2H, NCH_2), 1.82–1.74 (m, 2H, OCH$_2$CH_2), 1.54 (d, *J* = 7.2 Hz, 6H, 2 x CH_3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7 (C=O), 162.4 (d, $J_{C\text{-}F}$ = 248.0, CF), 141.5 (C), 138.4 (C), 134.6 (C), 133.3 (d, $J_{C\text{-}F}$ = 8.2 Hz, CH and C), 130.5 (CH), 128.8 (C), 128.7 (CH), 128.4 (CH), 128.3 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 126.6 (CH), 123.5 (CH), 121.9 (C), 119.6 (CH), 115.6 (d, $J_{C\text{-}F}$ = 21.9 Hz, CH), 59.9 (CH_2), 41.7 (CH_2), 34.3 (CH_2), 26.2 (CH), 21.7 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat) 3404.4, 2960.3, 1658.2, 1651.3, 1594.8, 1525.5 and 1507.3.

HRMS (MALDI) calculated for $C_{29}H_{29}FNaN_2O_2$ $[M+Na]^+$ 479.2105, found 479.2115.

3-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)propyl 2,4,6-triisopropylbenzoate (**294**)



293 **294**

To a stirred solution of triphenylphosphene (0.63 g, 2.41 mmol, 1.10 equiv), 5-(4-fluorophenyl)-1-(3-hydroxypropyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (**293**) (1.00 g, 2.19 mmol, 1.00 equiv) and 2,4,6-triisopropylbenzoic acid (0.63 g, 2.52 mmol, 1.15 equiv) in anhydrous THF (0.66 M, 3.32 mL) under a nitrogen atmosphere was added DIAD (0.47 mL, 2.41 mmol, 1.10 equiv) dropwise. The resulting reaction mixture was stirred at ambient temperature overnight before the volatiles were removed *in vacuo*. The crude residue was purified by column chromatography (Si_2O, pentane:Et_2O 80:20) to yield **294** (1.23 g, 82%) as a white foam.

R_f 0.67 (pentane:Et_2O 60:40)

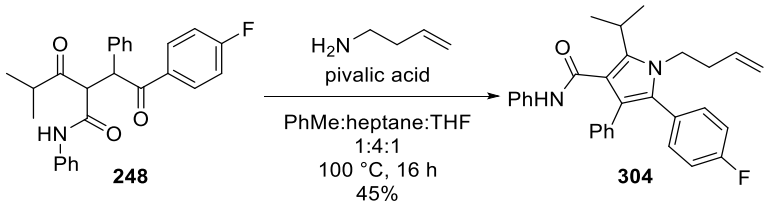
^{1}H NMR (500 MHz, $CDCl_3$) 7.20–7.11 (m, 9H, Ar*H*), 7.07–6.96 (m, 5H, Ar*H*), 6.86–6.79 (m, 2H, Ar*H*), 4.16 (t, *J* = 6.2 Hz, 2H, OC*H*$_2$), 3.99–3.96 (m, 2H, NC*H*$_2$), 3.47 (hept, *J* = 7.1 Hz, 1H, C*H*), 2.91 (hept, *J* = 6.8 Hz, 1H, C*H*), 2.74 (hept, *J* = 6.8 Hz, 2H, 2 x C*H*), 2.05–1.98 (m, 2H, OCH$_2$C*H*$_2$), 1.52 (d, *J* = 7.1 Hz, 6H, 2 x C*H*$_3$), 1.26 (d, *J* = 6.8 Hz, 6H, 2xC*H*$_3$), 1.20 (d, *J* = 6.8 Hz, 12H, 2 x ((C*H*$_3$)$_2$)) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (C=O), 164.7 (C=O), 162.3 (d, $J_{C\text{-}F}$ = 248.4 Hz, C), 150.4 (C), 144.7 (C), 141.5 (C), 138.3 (C), 134.5 (C), 133.0 (d, $J_{C\text{-}F}$ = 8.3 Hz, CH and C), 130.5 (CH), 130.0 (CH), 128.7 (C), 128.7 (CH), 128.4 (CH), 127.9 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 126.7 (CH), 123.6 (CH), 122.0 (C), 120.9 (CH), 119.6 (CH), 115.4 (d, $J_{C\text{-}F}$ = 21.5 Hz, CH), 62.1 (CH_2), 41.9 (CH_2), 34.4 (CH), 31.6 (CH), 30.8 (CH_2), 26.3 (CH), 24.1 (CH_3), 23.9 (CH_3), 21.7 (CH_3) ppm.

HRMS (ESI) calculated for $C_{45}H_{51}FN_2NaO_3$ $[M+Na]^+$ 709.3776, found 709.3790.

IR (ν_{max}/cm^{-1}, neat) 2961.1, 1725.4, 1667.8, 1595.2, 1526.1, 1509.5.

1-(But-3-en-1-yl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (**304**)



Pivalic acid (0.24 g, 2.40 mmol, 0.20 equiv) was added to a solution of 2-(2-(4-fluorophenyl)-2- oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**248**) (5.00 g, 12.0 mmol, 1.00 equiv) and but-3-en-1-amine (1.65 mL, 18.0 mmol, 1.50 equiv) in a mixture of toluene (5.90 mL), heptane (23.5 mL) and THF (5.90 mL). The reaction mixture was stirred at 120 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and diluted with H_2O (50 mL) and Et_2O (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane:Et_2O 5:1) to yield **304** (5.43 g, 62%) as a white solid.

R_f 0.52 (pentane:Et_2O 80:20)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.15 (m, 9H, Ar*H*), 7.08–7.04 (m, 2H, Ar*H*), 6.95–7.03 (m, 3H, Ar*H*), 6.86 (br. s, 1H, N*H*), 5.57 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H, C*H*=CH_2), 5.02–4.92 (m, 2H, CH=CH_2), 3.89 (m, 2H, NCH_2), 3.57 (sept, *J* = 7.2 Hz, C*H*(CH_3)$_2$), 2.27 (m, 2H, NCH_2CH_2), 1.54 (d, *J* = 7.2 Hz, 6H, CH(CH_3)$_2$) ppm.

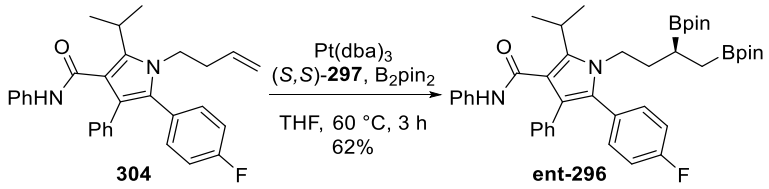
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (C=O), 162.4 (d, $J_{C\text{-}F}$ = 248.0, CF), 141.4 (C), 138.4 (C), 134.6 (C), 133.7 (CH=CH_2), 133.3 (d, $J_{C\text{-}F}$ = 8.2 Hz, CH and C), 130.5 (CH), 128.8 (C), 128.7 (CH), 128.3 (CH), 128.3 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 126.6 (CH), 123.5 (CH), 121.8 (C), 119.5 (CH), 117.3 (CH=CH_2), 115.5 (d, $J_{C\text{-}F}$ = 21.9 Hz, CH), 44.0 (NCH_2), 35.7 (NCH_2CH_2), 26.2 (CH(CH_3)$_2$), 21.7 (CH(CH_3)$_2$) ppm.

IR (ν_{max}/cm^{-1}, neat) 3392, 2963, 1656, 1529, 1218 and 755.

HRMS (ESI) calculated for $C_{30}H_{30}FN_2O$ $[M+H]^+$ 453.2337, found 453.2333.

MP 143 – 141 °C (Et_2O).

(*S*)-1-(3,4-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (**ent-296**)



$Pt(dba)_3$ (17.8 mg, 0.02 mmol, 3.00 mol%), (*S*,*S*)-**297** (36.0 mg, 0.04 mmol, 6.00 mol%) and B_2pin_2 (335 mg, 1.32 mmol, 2.00 equiv) were added to a flame-dried Schlenk-tube purged with N_2. Anhydrous THF (1.00 M, 0.66 mL) was added before sealing the flask and heating at 80 °C (oil bath) for 30 min. After cooling to ambient temperature, 1-(but-3-en-1-yl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (**304**) (300 mg, 0.66 mmol, 1.00 eq.) was added before re-sealing and heating for 16 h at 60 °C (oil bath). The solution was then cooled to ambient temperature and concentrated under reduced pressure. The crude residue was directly purified by flash column chromatography (SiO_2, pentane:Et_2O 5:1) to yield **ent-296** (287 mg, 62%) as a white foam.

R_f 0.24 (pentane:Et_2O 80:20)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.11 (m, 9H, Ar*H*), 7.08–7.03 (m, 2H, Ar*H*), 7.00–6.94 (m, 3H, Ar*H*), 6.85 (br. s, 1H, N*H*), 3.87 (dt, *J* = 13.0, 4.9 Hz, 1H, NC*H*$_a$H$_b$), 3.73 (dt, *J* = 13.0, 4.9 Hz, 1H, NCH$_a$*H*$_b$), 3.58–3.44 (m, 1H, C*H*(CH_3)$_2$), 1.84–1.71 (m, 1H, $NCH_2CH_aH_b$), 1.69–1.59 (m, 1H, $NCH_2CH_aH_b$), 1.54 (d, *J* = 7.1 Hz, 6H, CH(C*H*$_3$)$_2$), 1.22 (s, 12H, 2×C(C*H*$_3$)$_2$), 1.18 (s, 12H, 2 × C(C*H*$_3$)$_2$), 1.06–0.98 (m, 1H, C*H*Bpin), 0.81 (dd, *J* = 15.9, 9.1 Hz, 1H, CH$_a$*H*$_b$Bpin), 0.69 (dd, *J* = 15.9, 5.8 Hz, 1H, C*H*$_a$H$_b$Bpin) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0 (C=O), 161.1 (d, $J_{C\text{-}F}$ = 246.7 Hz, CF), 141.5 (C), 138.6 (C), 135.0 (C), 133.4 (d, $J_{C\text{-}F}$ = 8.9 Hz, CH and C), 130.6 (CH), 128.7 (C), 128.5 (CH), 128.3 (CH), 126.5 (CH), 123.5 (CH), 121.6 (C), 119.6 (CH), 115.3 (d, $J_{C\text{-}F}$ = 21.4 Hz, CH), 83.2 (d, $J_{C\text{-}F}$ = 9.3 Hz, C), 44.4 (NCH_2), 36.1 (NCH_2CH_2), 26.2 (CH_3), 25.0 (pinacol-CH_3), 24.8 (pinacol-CH_3), 21.7 (CH_3) ppm.

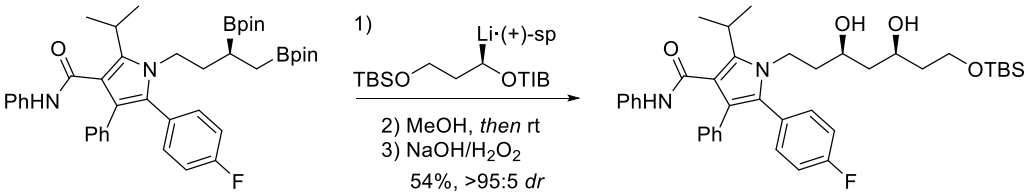
Carbon atoms next to boron not observed due to quadrupolar relaxation.

IR (ν_{max}/cm^{-1}, neat) 3411, 2976, 1669, 1509, 1370, 1311, 1220, 1140, 844 and 752.

HRMS (ESI) calculated for $C_{42}H_{53}B_2FN_2NaO_5$ $[M+Na]^+$ 729.4031, found 729.4040.

$[\alpha]_D^{24}$((c = 1.0, $CHCl_3$) –7.0.

1-((3R,5S)-7-((tert-Butyldimethylsilyl)oxy)-3,5-dihydroxyheptyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (**223**)



ent-296 **223**

3-((*t*-Butyldimethylsilyl)oxy)propyl 2,4,6-triisopropylbenzoate (**287**) (117.8 mg, 0.28 mmol, 2.00 equiv), (+)-sparteine (0.06 mL, 0.28 mmol, 2.00 equiv) and anhydrous Et_2O (0.23 M, 1.18 mL) were added to a flame-dried Schlenk-tube purged with N_2. The solution was cooled to −78 °C (dry ice/acetone) before adding *s*-BuLi (0.22 mL, 0.28 mmol, 2.00 equiv) dropwise over 5 min and leaving to react for 4 h at this temperature. **Ent-296** (100 mg, 0.14 mmol, 1.00 equiv) dissolved in anhydrous Et_2O (0.50 M, 0.28 mL) was added dropwise to the reaction mixture over 1 min before leaving to react for a further 1 h at the same temperature. MeOH (0.10 mL) was added dropwise before allowing the flask to warm to ambient temperature. Water (50 mL) was added and the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. THF (2 mL) and one crystal of BHT were added, before cooling to 0 °C (ice/water). A 2:1 *v:v* mixture of 3.00 M aqueous NaOH (2.74 mL) and 30% aqueous H_2O_2 (1.38 mL) was prepared at 0 °C (ice/water) and degassed by gently bubbling N_2 through the solution. This aqueous solution was added at once to the vigorously stirred reaction mixture, which was subsequently warmed to ambient temperature and allowed to react for 16 hr. Water (50 mL) was added and the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over MgSO4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane:Et_2O 50:50) to yield **223** (50 mg, 54%, >95:5 *dr*) as a white foam.

R_f 0.39 (Et_2O:pentane 60:40)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.13 (m, 9H, Ar*H*), 7.08–7.05 (m, 2H, Ar*H*), 7.01–7.69 (m, 3H, Ar*H*), 6.86 (s, 1H, N*H*), 4.16–4.08 (m, 2H, NC*H*aHb , O*H*), 4.05–3.98 (m, 2H, C*H*, O*H*), 3.93 (ddd, *J* = 14.8, 10.9, 5.3 Hz, 1H, NCHa*H*b), 3.88 (app. dt, *J* = 9.9, 4.4 Hz, 1H, OC*H*aHb), 3.80 (app. td, *J* = 10.1, 9.9, 3.2 Hz, 1H, OCHa*H*b), 3.75 (tdd, *J* = 9.9, 5.1, 3.1 Hz, 1H, C*H*), 3.58 (sept, *J* = 6.9 Hz, 1H, C*H*(CH_3)$_2$), 1.73–1.59 (m, 4H, NCH_2CH_2, OCH_2CH_2), 1.57–1.52 (d, *J* = 6.9 Hz, 6H, CH(CH_3)$_2$), 1.49–1.45 (m, 1H, OHCHCHa*H*b), 1.23–1.19 (m, 1H, OHCHCHaHb), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 6H, Si(CH_3)$_2$) ppm.

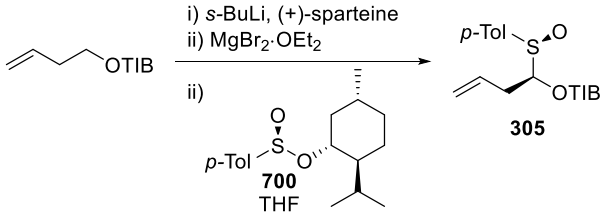
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8 (C=O), 162.2 (d, J_{C-F} = 247.6 Hz, CF), 141.6 (C), 138.4 (C), 134.7 (C), 133.2 (d, J_{C-F} = 7.8 Hz, CH and C), 130.5 (CH), 128.7 (C), 128.6 (CH), 128.4 (d, J_{C-F} = 3.5 Hz, C), 128.3 (CH), 126.5 (CH), 123.4 (CH), 121.7 (C), 119.5 (CH), 115.3 (d, J_{C-F} = 21.3 Hz, CH), 74.0 (CH), 69.9 (CH), 62.9 (OCH_2), 42.8 ($OHCHCH_2$), 41.4 (NCH_2), 39.2 (OCH_2CH_2), 26.1 (CH(CH_3)$_2$), 25.8 (CH_3), 21.6 (CH_3), 18.0 (C), –5.6 (CH_3) ppm.

IR (ν_{max}/cm^{-1}, neat) 3411, 2928, 2856, 1644, 1509, 1312, 1076 and 835.

HRMS (ESI) calculated for $C_{39}H_{53}FN_2O_4Si$ [M+H]+ 659.3675, found: 659.3681

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$**(** (c = 1.0, $CHCl_3$) +12.0.

<u>(*R*)-1-((l1-Oxidaneyl)(*p*-tolyl)-l3-sulfaneyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (**305**)</u>



According to a literature procedure,[65] *s*-BuLi (30.5 ml, 39.7 mmol, 1.20 equiv) was added dropwise to a stirred solution of but-3-en-1-yl 2,4,6-triisopropylbenzoate (10.0 g, 33.1 mmol, 1.00 equiv) and (+)-sparteine (9.12 ml, 39.7 mmol, 1.20 equiv) in anhydrous Et_2O (0.12 M, 275 ml) under N_2 at –78 °C (acetone/dry ice). The resulting reaction mixture was stirred at –78 °C for 1.5 h. Freshly prepared $MgBr_2{\cdot}OEt_2$ (49.6 mmol, 1.50 equiv) was added to the reaction dropwise *via* cannula and the resulting reaction mixture was stirred for 2 h at –78 °C. A solution of **700** (14.61 g, 49.6 mmol, 1.50 equiv) in anhydrous THF

(1.15 M, 43 ml) was added and the resulting reaction mixture was stirred for a further 1 h at –78 °C. The reaction mixture was then warmed to ambient temperature and stirred for 16 h. The reaction was diluted with a 2 M aqueous solution of HCl (100 ml) and Et_2O (100 ml) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 150 ml) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The aqueous phase was saved for (+)-sparteine recovery.

Sulfoxide **305** co-elutes with menthol and so the menthol was TMS protected to aid separation. The crude residue was stirred under high vacuum until it became a paste, at which point DCM (0.50 M, 66 ml) was added followed by NEt_3 (8.61 ml) and TMSCl (6.81 ml). The resulting mixture was stirred at ambient temperature for 2 h before being diluted with water (50 ml). The phases were separated, and the aqueous phase extracted with DCM (3 x 50 ml). The combined organic phases were dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude residue was purified using a biotage isolera one system (loading method: dry load (~25 g telos), snap ultra 200g, 0% to 10% EtOAc in hexane, 15 column volumes) to give the title compound (**305**) (9479.5 mg, 65%, >95:5 *dr*) as a white solid.

Preparation of $MgBr_2 \cdot OEt_2$:

To a flame dried 3 neck flask fitted with a reflux condenser under N_2 was charged oven dried Mg (3.13 g, 129 mmol) and anhydrous Et_2O (70 ml). To this stirred suspension was added 1,2-dibromomethane (0.1 ml) and the resulting suspension was gently heated with a heat gun (lowest setting) until the reaction initiated (typically ~5 sec). Following initiation, 1,2-dibromoethane (4.20 ml, 49.6 mmol (total volume 4.30 ml)) was added dropwise at a rate determined by the vigorousness of the reaction. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a colourless upper layer and a grey bottom layer. Both layers were transferred by cannula. The unreacted Mg was cooled to 0 °C (water/ ice) and quenched through the slow addition of an appropriate amount of a 2 M aqueous solution of HCl.

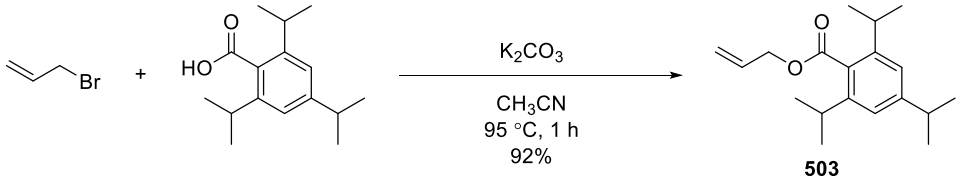
All data matched that reported in the literature.[65]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.38 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.04 (s, 2H, Ar*H*), 5.75 (dd, *J* = 10.0, 3.0 Hz, 1H, OC*H*), 5.67 (m, 1H, CH_2CH), 5.11–5.06 (m, 2H, $CHCH_2$), 2.91 (app sept, J = 6.6 Hz, 3H, 3xArC*H*), 2.72 (m, 1H,

OCHC*H*$_a$H$_b$), 2.44 (s, 3H, ArCH$_3$), 2.42 (m, 1H, OCHCH$_a$*H*$_b$), 1.28–1.23 (m, 18H, Ar(C(CH$_3$)$_2$)$_3$) ppm.

^{13}C NMR (126 MHz, CDCl$_3$) δ 170.1 (C=O), 150.7 (C), 145.1 (2C, C × 2), 141.6 (C), 137.2 (C), 131.3 (C), 130.0 (2C, C × 2), 128.7 (CH), 124.3 (2C, C × 2), 120.9 (2C, C × 2), 119.2 (CH$_2$), 91.3 (CH), 34.3 (CH), 31.4 (CH$_2$), 27.7 (2C, CH x 2), 24.3 (2C, CH$_3$ × 2), 24.1 (2C, CH$_3$ × 2), 23.8 (2C, CH$_3$ × 2), 21.3 (CH$_3$) ppm.

Allyl 2,4,6-triisopropylbenzoate (**503**)



503

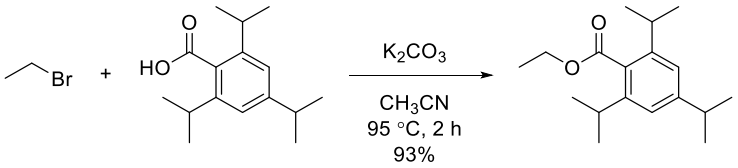
According to a literature procedure,[204] K$_2$CO$_3$ (5.60 g, 40.0 mmol, 2.00 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (5.12 g, 20.0 mmol, 1.00 equiv) in acetonitrile (0.33 M, 60 ml). The resulting suspension was stirred vigorously for 10 min before allyl bromide (5.76 ml, 40.0 mmol, 2.00 equiv) was added. The resulting reaction mixture was heated at 95 ºC (oil bath) for 1 h, at which point the reaction was deemed complete by TLC analysis. The reaction mixture was filtered (EtOAc) and the filtrate concentrated *in vacuo*. The residue was diluted with EtOAc (200 ml) and was successively washed with water (2 x 50 ml), brine (50 ml), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO$_2$, pentane:Et$_2$O 98:2) to afford the title compound (**503**) (5.33 g, 92%) as a colourless oil.

All spectral data matched that reported in the literature.[204]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.00 (s, 2H, 2 x Ar*H*), 6.02 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H, OCH$_2$C*H*), 5.41 (m, 1H, OCH$_2$CHC*H*$_a$H$_b$), 5.28 (m, 1H, OCH$_2$CHCH$_a$*H*$_b$), 2.89 (hept, *J* = 6.9 Hz, 1H, *p*ArC*H*,) 2.86 (sep, *J* = 6.9 Hz, 2H, 2 x *o*ArC*H*), 1.24 (d, *J* = 6.9 Hz, 18H, 3 x ArCH(C*H*$_3$)$_2$) ppm.

^{13}C NMR (101 MHz, CDCl$_3$) δ 170.5 (C=O), 150.2 (C), 144.8 (C), 132.0 (CH), 130.2 (C), 120.9 (CH), 119.0 (CH$_2$), 65.6 (CH$_2$), 34.4 (CH), 31.5 (CH), 24.1 (CH$_3$), 23.9 (CH$_3$) ppm.

Ethyl 2,4,6-triisopropylbenzoate



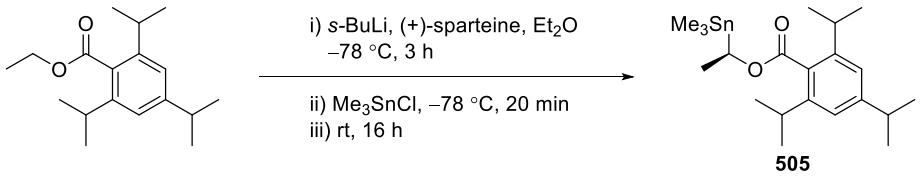
According to a literature procedure,[204] K_2CO_3 (11.13 g, 80.5 mmol, 2.00 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (10.0 g, 40.3 mmol, 1.00 equiv) in acetonitrile (0.33 M, 122 ml). The resulting suspension was stirred vigorously for 10 min before ethyl bromide (6.01 ml, 80.5 mmol, 2.00 equiv) was added. The resulting reaction mixture was heated at 95 ºC (oil bath) for 2 h. The reaction mixture was filtered through a pad of celite (EtOAc) and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane: Et_2O 98:2 to 95:5) to afford the title compound (10.35 g, 93%) as a colourless oil.

All spectral data matched that reported in the literature.[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H, Ar*H*), 4.38 (q, *J* = 7.2 Hz, 2H, OCH_2), 2.88 (m, 3H, 2 x *o*ArC*H* and *p*ArC*H*), 1.38 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.26 (d, *J* = 6.9 Hz, 12H, 2 x *o*ArCH(CH_3)$_2$), 1.25 (d, *J* = 6.9 Hz, 6H, *p*ArCH(CH_3)$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C=O), 150.1 (C), 144.7 (C), 130.6 (C), 120.8 (CH), 60.8 (CH_2), 34.4 (CH), 31.4 (CH), 24.1 (CH_3), 24.0 (CH_3), 14.3 (CH_3) ppm.

(*R*)-1-(Trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (**505**)



505

According to a literature procedure,[52] ethyl 2,4,6-triisopropylbenzoate (10.05 g, 36.36 mmol, 1.00 equiv) and (+)-sparteine (10.9 ml, 47.3 mmol, 1.30 equiv) were added to a flame dried Schlenk tube. The flask was evacuated and backfilled with N_2 three times. Anhydrous Et_2O (0.25 M, 181 ml) was added and the resulting solution was cooled to –78 ºC (acetone/ dry ice). *s*-BuLi (10.9 ml, 47.3 mmol, 1.30 equiv) was added dropwise and the resulting solution was stirred at –78 ºC for 3 h. Me_3SnCl (47.3 ml, 47.3 mmol, 1.30 equiv, 1.00 M in hexanes) was added dropwise and the resulting solution was stirred at –78 ºC for 20 min, and then at ambient temperature for 16 h. The reaction mixture was

quenched with 2 M aqueous solution of HCl (150 ml) and the phases were separated. The organic phase was washed with 2 M HCl (3 x 50 ml) and the combined aqueous phases were retained for (+)-sparteine recovery. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to an off white solid. The crude material was purified by recrystallisation in hot MeOH (3 ml/g) to afford the title compound (**505**) (8.304 g, 52%, 99.9:0.1 *er*) as white needles.

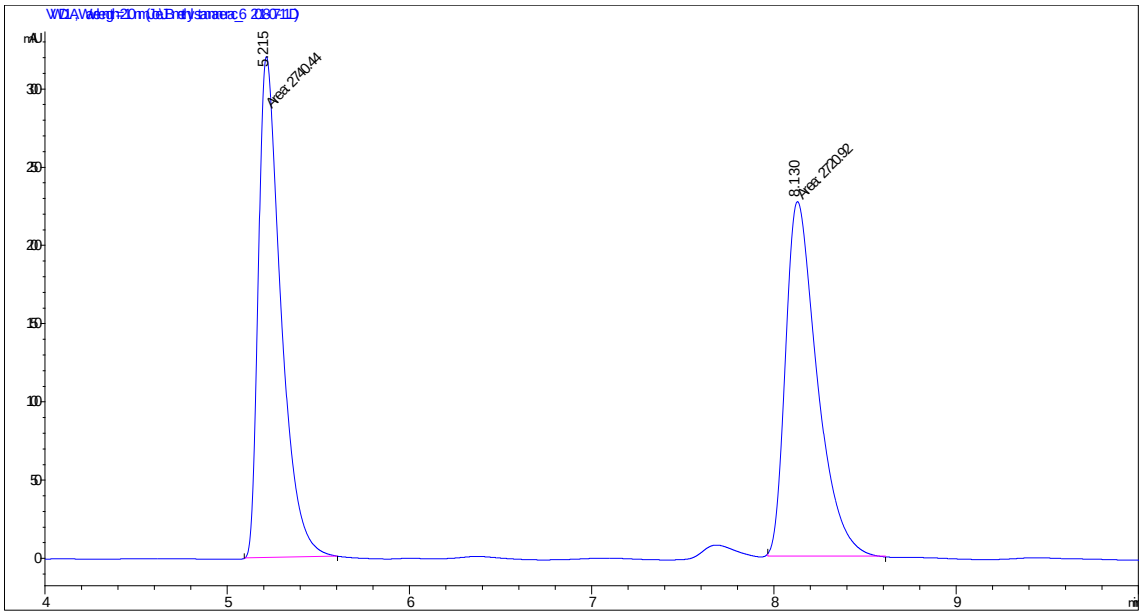
All data matched that reported in the literature.[52]

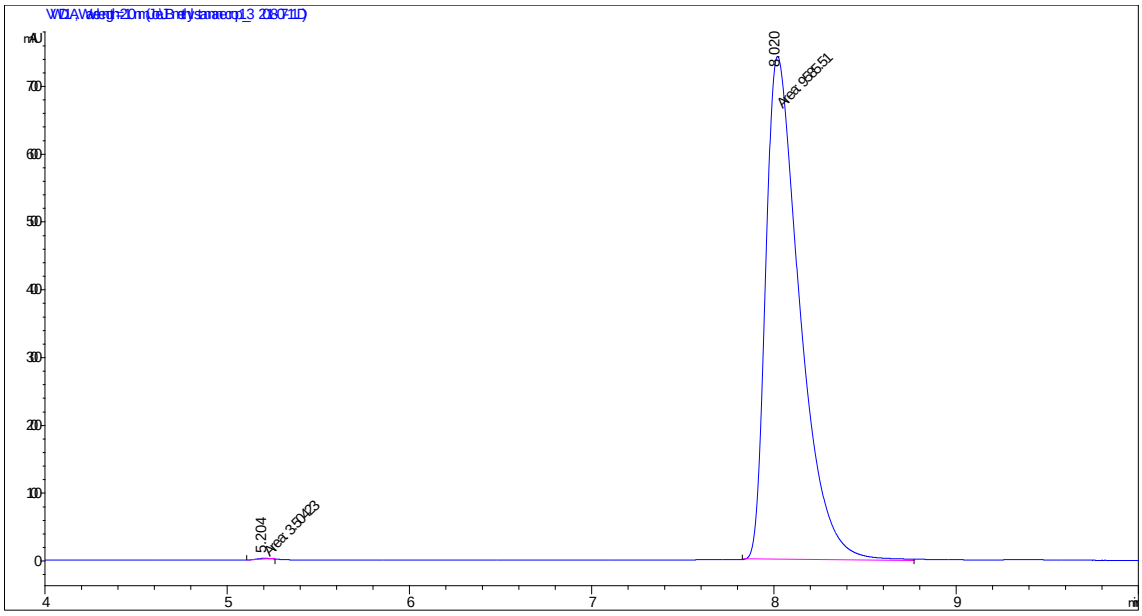
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 2H, 2xAr*H*), 5.04 (q, *J* = 6.9 Hz, 1H, OC*H*), 2.80–2.95 (m, 3H, 2 x *o*ArC*H* and *p*ArC*H*), 1.58 (m, 3H, OCHCH_3), 1.24 (d, *J* = 6.9 Hz, 18H, 3 x ArCH(CH_3)$_2$), 0.18 (s and d, *J* = 54.1 Hz and d, J = 51.8 Hz, 9H, Sn(Me)$_3$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (C=O), 149.9 (C), 144.8 (C), 130.8 (C), 120.8 (CH), 67.0 (CH), 34.4 (CH), 31.3 (CH), 24.3 (CH_3), 24.1 (CH_3), 24.0 (CH_3), 19.2 (CH_3), –9.9 (CH_3) ppm.

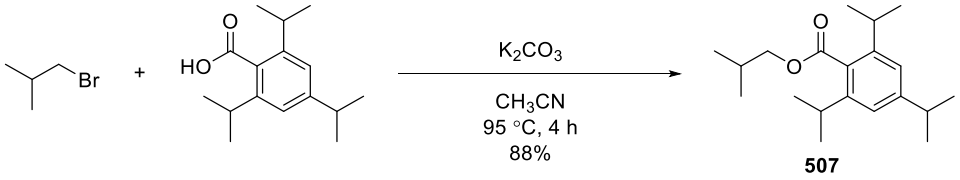
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ ($CHCl_3$, *c* = 1) +40. Literature[52] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ ($CHCl_3$, *c* = 1.1) +38.3.

Chiral HPLC (Diacel Chiralpak-IB with guard, hexane, 0.9 mL/min, rt, 210 nm) t_R = 5.1 min (minor), 8.1 min (major), *er* 99.9:0.1.





Isobutyl 2,4,6-triisopropylbenzoate (**507**)



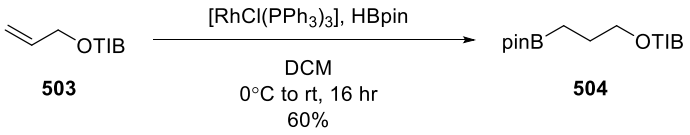
According to a modified literature procedure,[204] K_2CO_3 (5.60 g, 40.0 mmol, 2.00 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (5.12 g, 20.0 mmol, 1.00 equiv) in acetonitrile (0.33 M, 60 ml). The resulting suspension was stirred vigorously for 10 min before isobutyl bromide (4.40 ml, 40.0 mmol, 2.00 equiv) was added. The resulting reaction mixture was heated at 95 ºC (oil bath) for 4 h. The reaction mixture was filtered through a pad of celite (EtOAc) and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane:DCM 90:10 to 70:30) to afford the title compound (**507**) (5.35 g, 88%) as a colourless oil.

All data matched that reported in the literature.[205]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 x Ar*H*), 4.09 (d, *J* = 6.6 Hz, 2H, OCH_2), 2.95–2.80 (m, 3H, 3 x Ar*CH*), 2.03 (*app* non, *J* = 6.6 Hz, 1H, OCH_2CH), 1.25 (d, *J* = 6.9 Hz, 18H, 3 x $ArCH(CH_3)_2$), 0.99 (d, *J* = 6.6 Hz, 6H, 2 x CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C=O), 150.0 (C), 144.7 (C), 130.8 (C), 120.8 (CH), 71.3(CH_2), 34.4 (CH), 31.5 (CH), 27.7 (CH), 24.2 (CH_3), 24.0 (CH_3), 19.3 (CH_3) ppm.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)propyl 2,4,6-triisopropylbenzoate (**504**)



503 **504**

According to a modified literature procedure,[204] allyl 2,4,6-triisopropylbenzoate (**503**) (1.00 g, 3.47 mmol, 1.00 equiv) and Wilkinson's catalyst (32.1 mg, 3.47 μmol, 1.00 mol%) were added to a flame dried Schlenk tube. The flask was evacuated and backfilled with N_2 three times. DCM (1.00 M, 3.47 ml) was added and the resulting solution cooled to 0 ºC (water/ice). Pinacol borane (0.65 ml, 4.5 mmol, 1.3 equiv) was added dropwise over 5 min and the resulting solution was stirred at 0 ºC for 15 min before being warmed to ambient temperature and stirred for 16 h. The reaction mixture was then diluted with water (5 ml) and the phases separated. The aqueous phase was extracted with DCM (3 x 10ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane:Et_2O 96:4 to 94:6) to yield the title compound (**504**) (861 mg, 60%) as a white solid.

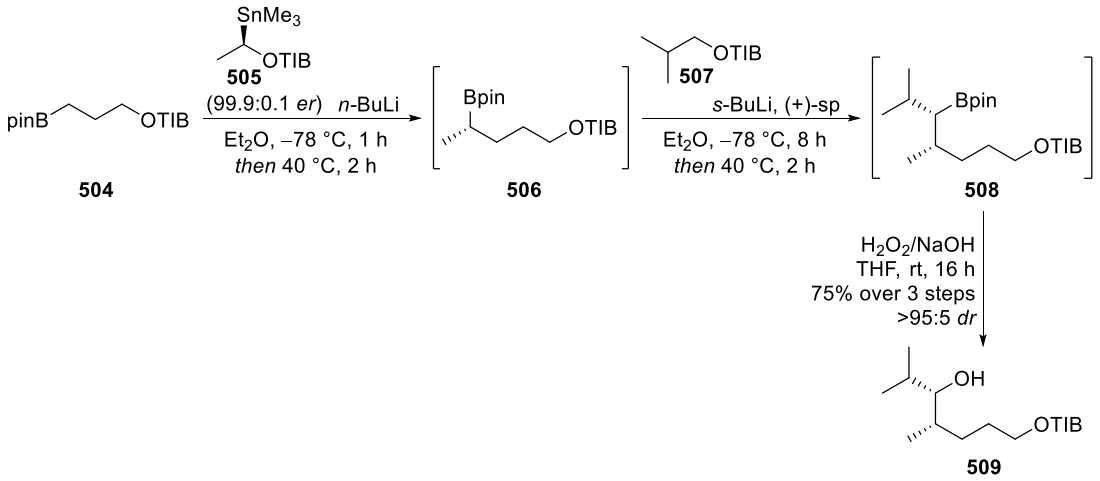
All data matched that reported in the literature.[204]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 2H, 2 x Ar*H*), 4.27 (t, *J* = 6.7 Hz, 2H, OC*H*$_2$), 2.92-2.81 (m, 3H, 3 x ArC*H*), 1.84 (tt, *J* = 7.9, 6.7 Hz, 2H, OCH$_2$C*H*$_2$), 1.24 (d, *J* = 7.0 Hz, 18H, 3 x ArCH(C*H*$_3$)$_2$), 1.23 (s, 12H, 4 x BOCC*H*$_3$), 0.87 (t, *J* = 7.9 Hz, 2H, BC*H*$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (C=O), 150.1 (C), 144.8 (C), 130.9 (C), 120.9 (CH), 83.3 (C), 66.9 (CH_2), 34.6 (CH), 31.6 (CH), 24.9 (CH_3), 24.3 (CH_3), 24.1 (CH_3), 23.3 (CH_2) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

(4*S*,5*S*)-5-Hydroxy-4,6-dimethylheptyl 2,4,6-triisopropylbenzoate (**509**)



(*R*)-1-(Trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (**505**) (5.43 g, 12.4 mmol, 1.30 equiv) was charged to a flame dried Schlenk tube under N_2. Anhydrous Et_2O (0.26 M, 48 ml) was added and the resulting solution was cooled to –78 °C (acetone/dry ice). *n*-BuLi (1.60 M in hexane, 7.73 ml, 12.4 mmol, 1.30 equiv) was added dropwise and the resulting reaction mixture was stirred at –78 °C for 1 h. A solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl 2,4,6-triisopropylbenzoate (**504**) (3.963 g, 9.52 mmol, 1.00 equiv) in anhydrous Et_2O (1.00 M, 9.52 ml) was added dropwise and the resulting solution was stirred at –78 °C for 1 h, at which point ^{11}B NMR showed full boronate complex formation. The reaction mixture was warmed to ambient temperature and then heated at 40 °C (oil bath) for 2 h, at which point ^{11}B NMR showed full consumption of the boronate complex. The reaction mixture was cooled to ambient temperature, filtered through a small pad of SiO_2 (Et_2O) and concentrated to yield boronic ester **506**, which was used immediately with no further purification.

Isobutyl 2,4,6-triisopropylbenzoate (**507**) (5.797 g, 19.0 mmol, 2.00 equiv) and (+)-sparteine (4.37 ml, 19.0 mmol, 2.00 equiv) were charged to a flame dried Schlenk tube, under N_2. Anhydrous Et_2O (0.26 M, 95 ml) was added and the resulting solution was cooled to –78 °C (acetone/dry ice). *s*-BuLi (1.30 M in hexane, 14.6 ml, 19.0 mmol, 2.00 equiv) was added dropwise and the resulting reaction mixture was stirred at –78 °C for 8 h. A solution of **507** (4.232 g, 9.52 mmol, 1.00 equiv) in anhydrous Et_2O (1.00 M, 9.52 ml) was added dropwise and the resulting solution was stirred at –78 °C for 1 h, at which point ^{11}B NMR showed full boronate complex formation. The reaction mixture was warmed to ambient temperature and then heated at 40 °C (oil bath) for 2 h, at which point

^{11}B NMR showed full consumption of the boronate complex. The reaction mixture was cooled to ambient temperature, quenched with a 2 M aqueous solution of HCl (150 ml) and the phases separated. The organic phase was washed with 2 M HCl (3x50 ml) and the combined aqueous phases were retained for (+)-sparteine recovery. The organic phase was dried over $MgSO_4$ filtered, and concentrated *in vacuo* to yield boronic ester **508**, which was used immediately with no further purification.

To a stirred solution of boronic ester **508** (4.766 g, 9.52 mmol, 1.00 equiv) in THF (0.15 M, 64 ml) at 0 °C (water/ice) was added a degassed mixture of $NaOH_{(aq)}$ (3.00 M, 61.8 ml) and H_2O_2 (30.9 ml) in one go. The reaction mixture was warmed to ambient temperature and stirred vigorously for 16 h. The reaction mixture was then diluted with water (10 ml) and Et_2O (10 ml) and the phases separated. The aqueous phase was extracted with Et_2O (3 x 20 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane:Et_2O 80:20) to yield the title compound (**509**) (2789 g, 75%, >95:5 *dr*) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 2H, Ar*H*), 4.31 (m, 2H, TIBOCH_2), 3.10 (m, 1H, C*H*OH), 2.93–2.81 (m, 3H, 3 x ArC*H*), 1.85–1.70 (m, 3H, OCH_2CH_2 and C*H*CHOH), 1.67 (m, 1H, $OCH_2CH_2CH_2CH$), 1.55–1.47 (m, 1H, $CHCH_aH_b$), 1.41–1.32 (m, 1H, $CHCH_aH_b$), 1.25 (d, *J* = 6.9 Hz, 12H, 2 x *o*ArC(CH_3)$_2$), 1.25 (d, *J* = 7.0 Hz, 6H, *p*ArC(CH_3)$_2$), 0.97 (d, *J* = 6.6 Hz, HOCHCHCH_3), 0.88 (*app* t, 6H, 2 x CH_3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (C=O), 150.2 (C), 144.9 (C), 130.8 (C), 121.0 (CH), 80.2 (CH), 65.4 (CH_2), 34.9 (CH), 34.6 (CH), 31.7 (CH), 31.2 (CH), 30.8 (CH_2), 26.6 (CH_2), 24.3 (CH_3), 24.1 (CH_3), 19.5 (CH_3), 18.8 (CH_3), 12.9 (CH_3) ppm.

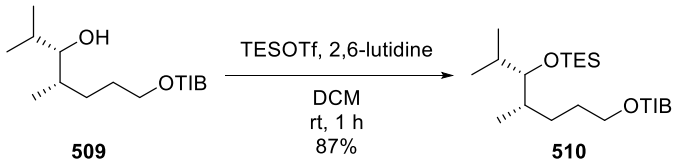
HRMS (ESI) calculated for $C_{25}H_{42}NaO_3$ $[M+Na]^+$ 413.3026, found 413.3017.

IR (ν_{max}/cm^{-1}, neat) 3547.3, 2959.0, 2869.9, 1724.0, 1606.3, 1461.7 and 1251.6.

R_f 0.23 (4:1 pentane:Et_2O).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ ($CHCl_3$, *c* = 1) –3.

(4*S*,5*S*)-4,6-Dimethyl-5-((triethylsilyl)oxy)heptyl-2,4,6-triisopropylbenzoate (**510**)



509 **510**

Triethylsilyltrifluoromethanesulfonate (0.26 ml, 1.13 mmol, 1.20 equiv) and 2,6-lutidine (0.22 ml, 1.88 mmol, 2.00 equiv.) were added to a stirred solution of (4*S*,5*S*)-5-hydroxy-4,6-dimethylheptyl 2,4,6-triisopropylbenzoate (**509**) (365.4 mg, 0.94 mmol, 1.00 equiv.) in anhydrous DCM (0.34 M, 2.80 ml) at –78 °C (acetone/dry ice). The resulting solution was stirred at –78 °C for 1 h, at which point TLC analysis suggested full consumption of the starting material. The reaction was diluted with water (10 ml) and the phases separated. The aqueous phase was extracted with DCM (3x20ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, pentane:Et_2O 98:2) to yield the title compound (**510**) (414 mg, 87%, >95:5 *dr*) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 2H, Ar*H*), 4.28 (m, 2H, TIBOCH_2), 3.24 (dd, *J* = 6.1, 3.6 Hz, 1H, C*H*OH), 2.93–2.81 (m, 3H, 3 x ArC*H*), 1.86–1.65 (m, 3H, OCH_2CH_2 and $OCH_2CH_2CH_2CH$), 1.61 (m, 1H, TESOCHC*H*$(CH_3)_2$), 1.48 (m, 1H, $OCH_2CH_2CH_aH_b$), 1.32–1.24 (m, 19H, 3 x ($ArCH(CH_3)_2$) and $OCH_2CH_2CH_aH_b$), 0.97 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.91–0.86 (m, 9H, $OCHCH(CH_3)_2$) and $CHCH_3$), 0.62 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (C=O), 150.2 (C), 144.8 (C), 130.8 (C), 121 (CH), 81.6 (CH), 65.5 (CH_2), 36.2 (CH), 34.6 (CH), 31.8 (CH), 31.6 (CH), 31.1 (CH_2), 27.0 (CH_2), 24.3 (CH_3), 24.1 (CH_3), 20.2 (CH_3), 19.0 (CH_3), 14.3 (CH_3), 7.3 (CH_3), 5.8 (CH_2) ppm.

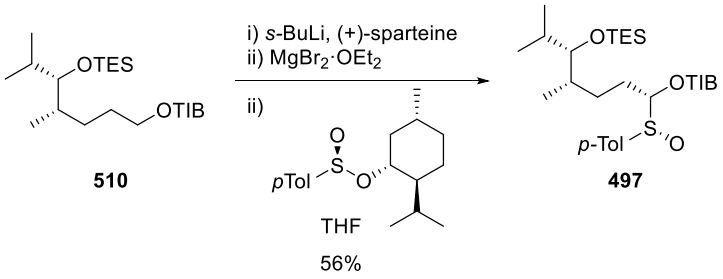
HRMS (ESI) calculated for $C_{31}H_{57}O_3Si$ $[M+H]^+$ 505.4071, found 505.4050.

IR (ν_{max}/cm^{-1}, neat) 3579.0, 2956.3, 2873.7, 1726.1, 1606.5, 1462.5 and 1249.9.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ ($CHCl_3$, *c* = 1) –4.

$\mathbf{R}_f$ 0.57 (98:2 pentane:Et_2O).

(1*R*,4*S*,5*S*)-1-((λ^1-Oxidaneyl)(*p*-tolyl)-l3-sulfaneyl)-4,6-dimethyl-5-((triethylsilyl)oxy)heptyl 2,4,6-triisopropylbenzoate (**497**)



According to a modified literature procedure,[65] *s*-BuLi (1.3 M in hexane, 6.3 ml, 8.1 mmol, 1.3 equiv) was added dropwise to a stirred solution of benzoate **510** (3.147 g, 6.23 mmol, 1.00 equiv) and (+)-sparteine (1.86 ml, 8.10 mmol, 1.30 equiv) in anhydrous Et_2O (0.25 M, 25 ml) under N_2 at –78 °C (acetone/dry ice). The resulting reaction mixture was stirred at –78 °C for 3 h. Freshly prepared $MgBr_2{\cdot}OEt_2$ (9.35 mmol, 1.50 equiv) was added to the reaction dropwise *via* cannula and the resulting reaction mixture was stirred for 2 h at –78 °C. A solution of ((((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)(*p*-tolyl)-λ^3-sulfaneyl)-λ^1-oxidane (2.754 g, 9.35 mmol, 1.50 equiv) in anhydrous THF (1.15 M, 8.13 ml) was added and the resulting reaction mixture was stirred for a further 1 h at –78 °C. The reaction mixture was then warmed to ambient temperature and stirred for 16 h. The reaction was diluted with a 2 M aqueous solution of HCl (30 ml) and Et_2O (30 ml) and the phases separated. The aqueous phase was extracted with Et_2O (3 x 50ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* and the aqueous phase was saved for (+)-sparteine recovery. The crude residue was purified using a biotage isolera one system (loading method: dry load (~ 10g Telos), snap ultra 50 g, 0% to 20% Et_2O in pentane, 13 column volumes) to give the title compound (**497**) (224 g, 56%, >95:5 *dr*) as a colourless oil.

Preparation of $MgBr_2{\cdot}OEt_2$:

To a flame dried 3 neck flask fitted with a reflux condenser under N_2 was charged oven dried Magnesium turnings (682 mg, 28.1 mmol) and anhydrous Et_2O (14.4 ml). To this stirred suspension was added 1,2-dibromomethane (0.1 ml) and the resulting suspension was gently heated with a heat gun (lowest setting) until the reaction initiated (typically ~5 sec). Following initiation, 1,2-dibromoethane (0.71 ml, 9.35 mmol (total volume 0.81 ml)) was added dropwise at a rate determined by the vigorousness of the reaction. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a

colourless upper layer and a grey bottom layer. Both layers were transferred by cannula. The unreacted Magnesium turnings were cooled to 0 °C (water/ice) and quenched through the slow addition of 2 M $HCl_{(aq)}$.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.37 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.05 (s, 2H, Ar*H*), 5.63 (dd, *J* = 10.2, 2.6 Hz, 1H, OC*H*S), 3.11 (dd, *J* = 5.9, 3.5 Hz, 1H, TESOC*H*), 2.99–2.88 (m, 3H, 3 x ArC*H*), 2.43 (s, 3H, ArCH_3), 1.95 (dtd, *J* = 15.0, 10.3, 4.9 Hz, 1H, TIBOCHC$H_a$$H_b$), 1.66–1.57 (m, 2H, TESOCHC*H*$(CH_3)_2$ and TIBOCHC$H_a$$H_b$), 1.44 (m, 1H, TIBOCHC$H_2CH_2$C*H*), 1.31–1.24 (m, 20H, ArCH(CH_3)$_3$ and TIBOCHCH_2CH_2), 1.27 (d, *J* = 6.9 Hz, 12H, 2 x *o*ArCH(CH_3)$_2$), 0.86 (t, *J* = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 0.80 (dd, *J* = 6.8, 5.6 Hz, 6H, TESOCHCH(CH_3)$_2$), 0.68 (d, *J* = 6.8 Hz, 3H, TESOCHCHCH_3), 0.45 (qd, *J* = 7.9, 3.6 Hz, 6H, Si(C$H_2$$CH_3$)$_3$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (C=O), 151.0 (C), 145.3 (C), 141.6 (C), 137.7 (C), 130.1 (CH), 129.0 (C), 124.4 (CH), 121.2 (CH), 93.3 (CH), 80.6 (CH), 36.4 (CH), 34.6 (CH), 31.8 (CH), 31.6 (CH), 29.2 (CH_2), 24.6 (CH_3), 24.4 (CH_3), 24.1 (CH_3), 21.6 (CH_3), 21.3 (CH_2), 20.4 (CH_3), 19.0 (CH_3), 14.4 (CH_3), 7.2 (CH_3), 5.6 (CH_2) ppm.

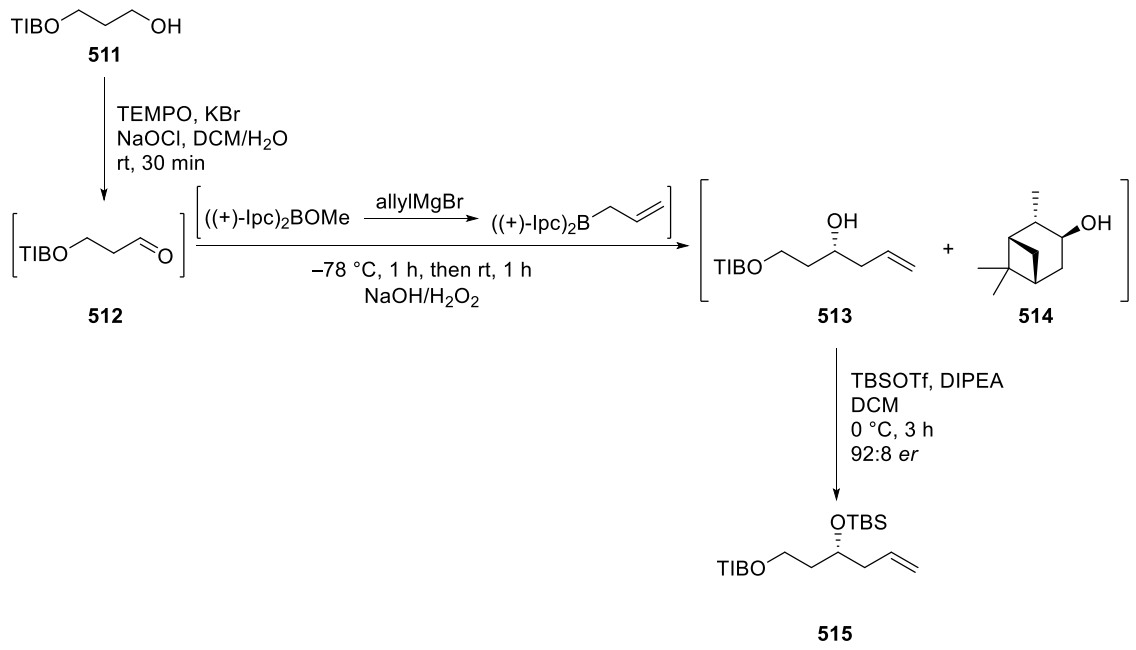
HRMS (ESI) calculated for $C_{38}H_{62}NaO_4SSi$ $[M+H]^+$ 665.4030, found 665.4021.

IR (ν_{max}/cm^{-1}, neat) 2958.9, 2873.8, 1732.7, 1606.1 1460.1, 1233.6 and 1045.2.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ ($CHCl_3$, *c* = 0.5) –94.

$\mathbf{R}_f$ 0.30 (90:10 pentane:Et_2O).

(*R*)-3-((tert-butyldimethylsilyl)oxy)hex-5-en-1-yl 2,4,6-triisopropylbenzoate (**515**)



Oxidation of alcohol **511**

According to a modified literature procedure.[206] To a stirred solution of alcohol **511** (1.51. g, 4.94 mmol, 1.00 equiv) in DCM (0.80 M, 6.2 ml) at 0 °C was added sequentially TEMPO (7.66 mg, 49.0 µmol, 1.00 mol%) as a solution in DCM (0.008 M, 6.18 ml), KBr (58.3 mg, 0.49 mmol, 10.0 mol%) as a solution in H_2O (0.50 M, 0.98 ml) and $NaOCl \cdot 5H_2O$ (1.02 g, 6.17 mmol, 1.25 equiv) as a solution in H_2O (0.35 M, 17.6 ml). The resulting biphasic mixture was stirred vigorously at ambient temperature for 30 min. After this time the organic phase was separated, dried over $MgSO_4$ and filtered through a small silica plug washing with Et_2O (15 ml). The filtrate was diluted with anhydrous THF (0.50 M, 9.88 ml) and concentrated at ambient temperature until only the volume of THF remained to yield aldehyde **512** as a rough 0.5 M solution in THF.

Allylboration

According to a modified literature procedure,[206] allylMgBr (1.00 M in Et_2O, 14.8 ml, 14.8 mmol. 3.00 equiv) was added to a stirred solution of (+)-Ipc_2BOMe (4.68 g, 14.8 mmol, 3.00 equiv) in anhydrous Et_2O (0.33 M, 14.8 ml) under an N_2 atmosphere at 0 °C (water/ice). The resulting mixture was warmed to ambient temperature and stirred for 1 h before the volatile components were removed under high vacuum. Pentane (20 ml) was added and the mixture was stirred vigorously for 30 sec before the stirring was stopped and the solids were allowed to settle. The pentane was transferred to a separate flask

through a sintered cannulation needle and the above process was repeated a further two times. The combined pentane extracts were then concentrated under high vacuum. The resulting residue was diluted with anhydrous Et_2O (0.33 M, 14.8 ml) and was cooled to –100 °C (MeOH/$N_{2(l)}$), at which point aldehyde **512** was added dropwise as a rough 0.5 M solution in THF. The reaction was stirred at –100 °C for 1 h, warmed to –78 °C and stirred for a further 1 h at –78 °C (acetone/dry ice). MeOH (HPLC grade, 10 ml) was added and the reaction was warmed to ambient temperature. NaOH (3.0 M aqueous solution, 12 ml) and H_2O_2 (6.0 ml) were added and the resulting mixture heated to reflux for 1 h. The reaction mixture was cooled to ambient temperature and Et_2O (50 ml) was added. The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 50 ml). The combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, pentane:Et_2O 80:20) to give secondary alcohol **513** as an inseparable mixture with (+)-isopinocampheol (**514**).

Silyl ether protection

To a stirred solution of secondary alcohol **513** and (+)-isopinocampheol (**514**) (4.69 g. 13.5 mmol. 1.00 equiv) in anhydrous DCM (0.10 M, 135 ml) under an N_2 atmosphere at 0 °C was added DIPEA (3.50 ml, 20.3 mmol, 1.50 equiv) dropwise followed by the dropwise addition of TBSOTf (3.72 ml, 16.2 mmol, 1.20 equiv). The resulting mixture was warmed to ambient temperature and stirred for 3 h. The reaction was diluted with H_2O (75 ml) and the phases were separated. The aqueous phase was extracted with DCM (3 x 100 ml) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, pentane: removal of TBS-protected isopinochampheol, then pentane:Et_2O 98:2) to yield **515** (1.62 g, 71%, 92:8 *er*) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, Ar*H*), 5.79 (m, 1H, alkene-C*H*), 5.09–5.03 (m, 2H, alkene-CH_2), 4.45 (ddd, *J* = 10.9, 6.9, 5.6 Hz, 1H, TIBOCH_aH_b), 4.33 (ddd, *J* = 10.9, 7.6, 6.5 Hz, 1H, TIBOCH_aH_b), 3.88 (m. 4.1 Hz, 1H, TBSOC*H*), 2.93–2.79 (m, 3H, 3xArC*H*), 2.26 (ddt, *J* = 7.1, 5.8, 1.2 Hz, 2H, alkene-CHCH_2), 1.91 (dddd, *J* = 14.4, 7.6, 6.9, 4.1 Hz, 1H, TIBOCH_2CH_aH_b), 1.82 (dddd, *J* = 14.4, 7.7, 6.5, 5.6 Hz, 1H, TIBOCH_2CH_aH_b), 1.24 (m, 18H, 3 x ArCH(CH_3)$_2$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.2 (C), 144.9 (C), 134.6 (CH), 130.7 (C), 121.0 (CH), 117.5 (CH_2), 69.0 (CH), 62.1 (CH_2), 42.4 (CH_2), 35.8 (CH_2), 34.6 (CH), 31.7 (CH), 26.0 (CH_3), 24.4 (CH_3), 24.3 (CH_3), 24.1 (CH_3), 18.2 (C), –4.2 (CH_3), –4.6 (CH_3) ppm.

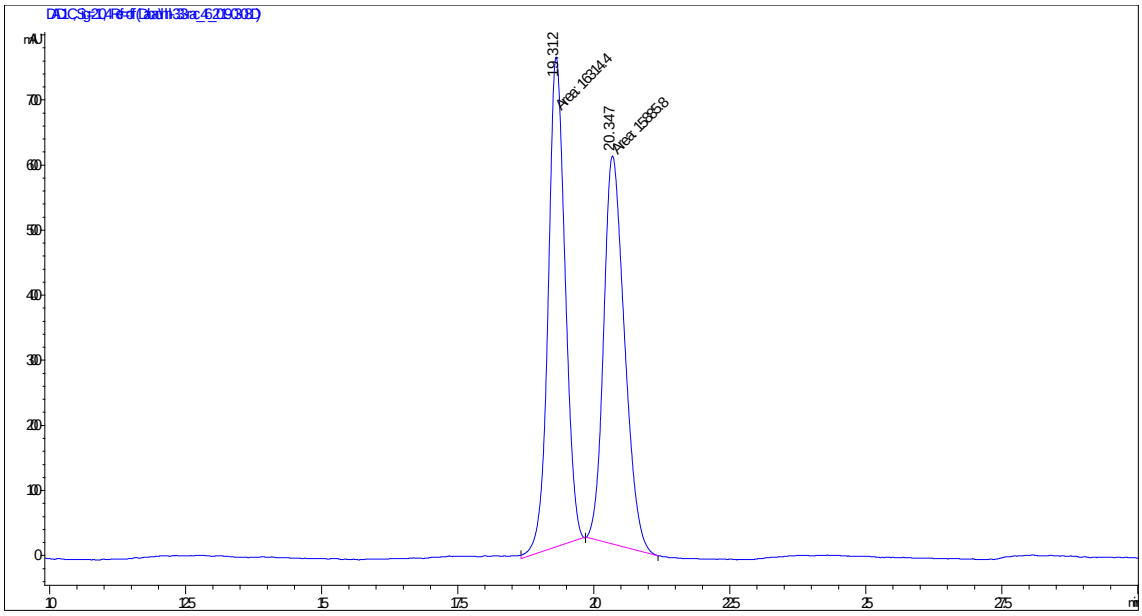
HRMS (ESI) calculated for $C_{28}H_{48}NaO_3Si$ $[M+Na]^+$ 483.3265, found 483.3267.

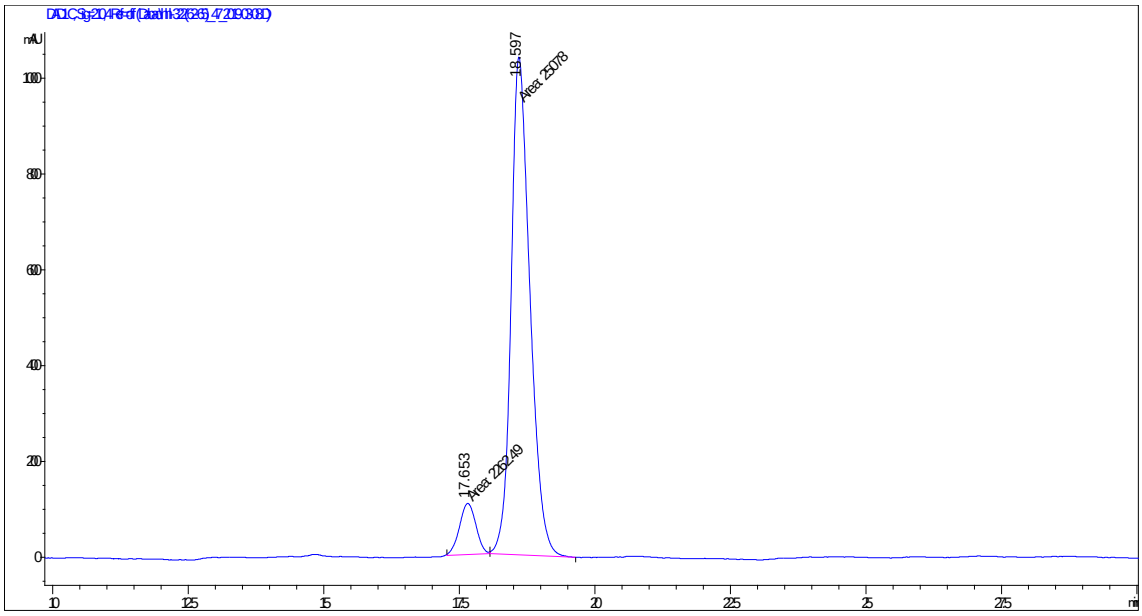
IR (ν_{max}/cm^{-1}, neat) 2958.7, 2928.9, 2858.2, 1725.7, 1250.5 and 1074.3.

$[\alpha]_D^{23}$ $CHCl_3$, *c* = 1) –8

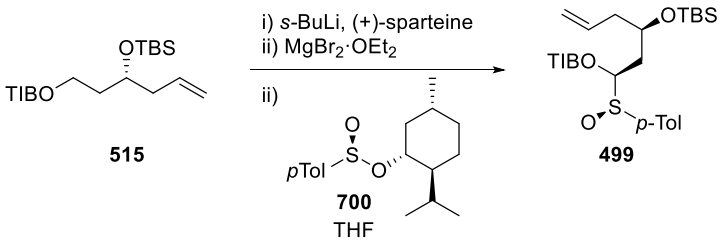
R_f 0.66 (2:98 Et_2O:pentane)

Chiral HPLC Chiral separation was achieved by deprotecting a small aliquot of **515** to give secondary alcohol **513** (Diacel Chiralpak-IA (25cm) with guard, hexane:IPA 99:1, 1.0 mL/min, rt, 210 nm) t_R = 17.7 min (minor), 18.6 min (major), *er* = 92:8.





(1*R*,3*R*)-1-((l1-Oxidaneyl)(p-tolyl)-l3-sulfaneyl)-3-((*tert*-butyldimethylsilyl)oxy)hex-5-en-1-yl 2,4,6-triisopropylbenzoate (**499**)



According to a modified literature procedure,[65] *s*-BuLi (2.52 ml, 3.28 mmol, 1.30 equiv) was added dropwise to a stirred solution of benzoate **515** (1.16 g, 2.52 mmol, 1.00 equiv) and (+)-sparteine (0.75 ml, 3.28 mmol, 1.30 equiv) in anhydrous Et_2O (0.25 M, 10.1 ml) under N_2 at –78 °C (acetone/dry ice). The resulting reaction mixture was stirred at –78 °C for 3 h. Freshly prepared $MgBr_2 \cdot OEt_2$ (3.78 mmol, 1.50 equiv) was added to the reaction dropwise *via* cannula and the resulting reaction mixture was stirred for 2 h at –78 °C. A solution of **700** (1.11 g, 3.78 mmol, 1.50 equiv) in anhydrous THF (1.15 M, 3.29 ml) was added and the resulting reaction mixture was stirred for a further 1 h at –78 °C. The reaction mixture was then warmed to ambient temperature and stirred for 16 h. The reaction was diluted with a 2 M aqueous solution of HCl (30 ml) and Et_2O (30 ml) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 50 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* and the aqueous phase was saved for (+)-sparteine recovery.

Sulfoxide **499** co-elutes with menthol and so the menthol was TMS protected to aid separation. The crude residue was stirred under high vacuum until it became a paste, at which point DCM (0.50 M, 5.0 ml) was added followed by NEt_3 (0.52 ml) and TMSCl (0.43 ml). The resulting mixture was stirred at ambient temperature for 2 h before being diluted with water (5.0 ml). The phases were separated and the aqueous phase extracted with DCM (3 x 10 ml). The combined organic phases were dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude residue was purified using a biotage isolera one system (loading method: dry load (~2.5 g telos), snap ultra 50g, 0% to 20% Et_2O in pentane, 25 column volumes) to give the title compound (**499**) (935.8 mg, 62%, >95:5 *dr*) as a white solid.

Preparation of $MgBr_2{\cdot}OEt_2$:

To a flame dried 3 neck flask fitted with a reflux condenser under N_2 was charged oven dried Mg (238.9 mg, 9.83 mmol) and anhydrous Et_2O (6.30 ml). To this stirred suspension was added 1,2-dibromomethane (0.05 ml) and the resulting suspension was gently heated with a heat gun (lowest setting) until the reaction initiated (typically ~5 sec). Following initiation, 1,2-dibromoethane (0.28 ml, 3.78 mmol (total volume 0.33 ml)) was added dropwise at a rate determined by the vigorousness of the reaction. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a colourless upper layer and a grey bottom layer. Both layers were transferred by cannula. The unreacted Mg was cooled to 0 °C (water/ice) and quenched through the slow addition of an appropriate amount of a 2 M aqueous solution of HCl.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2, 2H, Ar*H*), 7.35 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.06 (s, 2H, Ar*H*), 5.79 (dd, *J* = 10.3, 1.4 Hz, 1H, TIBOC*H*), 5.63 (m, 1H, alkene-C*H*), 5.04–4.99 (m, 2H, alkene-CH_2), 3.71 (m, 1H, TBSOC*H*), 3.01 (hept, *J* = 6.9 Hz, 2H, 2 x *o*ArC*H*), 2.92 (hept, *J* = 6.9 Hz, 1H, *p*ArC*H*), 2.41 (s, 3H, ArCH_3), 2.23 (m, 1H, alkene-CHCH_aH$_b$), 2.15 (m, 1H, alkene-CHCH$_a$$H_b$), 2.00 (ddd, *J* = 15.0, 10.3, 1.8 Hz, 1H, TIBOCHCH_aH$_b$), 1.69 (ddd, *J* = 15.0, 10.1, 1.4 Hz, 1H, TIBOCHCH$_a$$H_b$), 1.32–1.25 (m, 18H, 3xArCH(CH_3)$_2$), 0.67 (s, 9H, SiC(CH_3)$_3$), –0.05 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (C=O), 151.0 (C), 145.5 (C), 141.5 (C), 137.7 (C), 133.5 (CH), 130.1 (CH), 129.0 (C), 124.3 (CH), 121.2 (CH), 118.3 (CH_2), 91.9 (CH), 68.0 (CH), 42.9 (CH_2), 34.6 (CH), 31.8 (CH), 30.9 (CH_2), 25.7 (CH_3), 24.6 (CH_3), 24.4 (CH_3), 24.0 (CH_3), 21.5 (CH_3), 17.8 (C), –3.9 (CH_3), –4.6 (CH_3) ppm.

HRMS (ESI) calculated for $C_{35}H_{54}NaO_4SSi$ $[M+Na]^+$ 621.3404, found 621.3411.

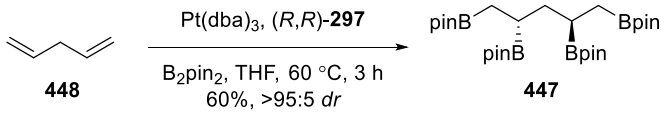
IR (ν_{max}/cm^{-1}, neat) 2959.6, 2929.3, 1733.2, 1462.0, 1363.7, 1235.7 and 1043.3.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CHCl_3$, *c* = 0.5) –43.

$\mathbf{R_f}$ 0.24 (1:9 Et_2O:pentane).

2,2',2'',2'''-((2*R*,4*R*)-Pentane-1,2,4,5-tetryl)tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**447**)

The characterisation of tetra(boronic ester) ***447*** *was performed by Dr Alexander Fawcett and is included for completeness.*



$Pt(dba)_3$ (174 mg, 0.19 mmol, 1.00 mol%), (*R*,*R*)-**297** (211 mg, 0.23 mmol, 1.20 mol%) and B_2pin_2 (10.32 g, 40.63 mmol, 2.10 equiv) were dissolved in THF (20.0 ml) before sealing the flask and heating to 80 °C (oil bath) for 30 min. After cooling to ambient temperature 1,4-pentadiene (**448**) (2.00 ml, 19.4 mmol, 1.00 equiv) was quickly added before resealing the vessel and heating for 16 h at 60 °C (oil bath). The solution was then cooled to ambient temperature and concentrated *in vacuo*. The crude residue was directly purified by flash column chromatography (SiO_2, pentane:Et_2O 80:20) to yield tetra(boronic ester) **447** (9.94 g, 89%, 95:5 *dr*) as a colourless solid. The solid was recrystallized (pentane; 0.80 ml/g; freezer overnight) to yield tetra(boronic ester) (**447**) (6.68 g, 60%, >95:5 *dr*) as a colourless crystalline solid.

$\boldsymbol{R_f}$ 0.19 (85:15 pentane:Et_2O)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.7 Hz, 2H, CH(C*H*$_2$)CH), 1.18 (s, 48H, CH_3), 1.31-1.03 (m, C*H*Bpin, 2H), 0.80 (dd, *J* = 15.8, 5.4 Hz, 2H, *H*^{a}H^{b}CBpin), 0.71 (dd, *J* = 15.8, 9.8 Hz, 2H, H^a*H*^{b}CBpin) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 83.0 (*C*(CH_3)$_2$), 82.8 (*C*(CH_3)$_2$), 37.0 (CH(*C*H_2)CH), 25.2 (CH_3), 25.2 (CH_3), 25.1 (CH_3), 25.0 (CH_3), 17.2 (CHBpin), 12.5 (CH_2Bpin) ppm.

IR (ν_{max}/cm^{-1}, neat) 2977, 2928, 1378, 1360, 1309, 1269, 1140, 968, 848 and 667.

HRMS (ESI) calculated for $C_{29}H_{56}B_4O_8Na$ $[M+Na]^+$ 599.4259, found: 599.4251.

m.p. 100–104 °C (pentane).

$[\alpha]_D^{24}$ ($CHCl_3$, *c* = 5.0) +0.4.

Crystal Structure

```
Bond precision:  C-C = 0.0030 A          Wavelength=0.71073

Cell:           a=9.2971(2)    b=15.6157(4)          c=12.1000(3)
                alpha=90       beta=95.4976(13)      gamma=90
Temperature:    100 K

                Calculated                Reported
Volume          1748.61(7)                1748.61(7)
Space group     P 21                      P 1 21 1
Hall group      P 2yb                     P 2yb
Moiety formula  C29 H56 B4 O8             C29 H56 B4 O8
Sum formula     C29 H56 B4 O8             C29 H56 B4 O8
Mr              575.98                    575.97
Dx,g cm-3       1.094                     1.094
Z               2                         2
Mu (mm-1)       0.075                     0.075
F000            628.0                     628.0
F000'           628.30
h,k,lmax        12,20,15                  12,20,15
Nref            8355[ 4330]               8051
Tmin,Tmax       0.959,0.965               0.669,0.746
Tmin'           0.955

Correction method= # Reported T Limits: Tmin=0.669 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 1.86/0.96      Theta(max)= 27.917

R(reflections)= 0.0369( 7353)     wR2(reflections)= 0.0925( 8051)

S = 1.021                 Npar= 386
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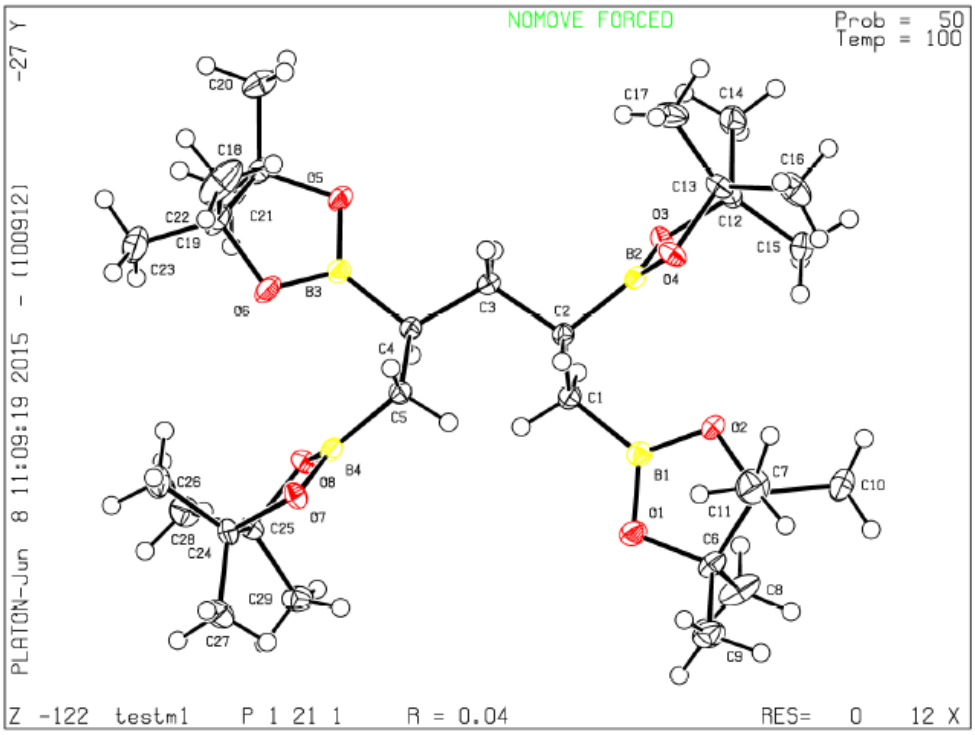
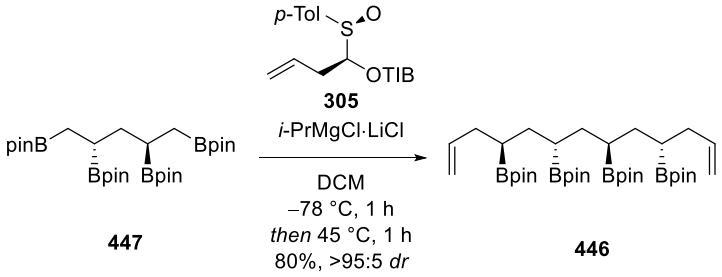


2,2',2",2"'-((4*R*,6*S*,8*S*,10*R*)-Trideca-1,12-diene-4,6,8,10-tetrayl)tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**446**)



i-PrMgCl·LiCl (1.17 M in THF, 5.00 ml, 5.90 mmol, 3.40 equiv) was added to a solution of tetra(boronic ester) **447** (1.00 g, 1.74 mmol, 1.00 equiv) and sulfoxide **305** (2448 mg, 5.56 mmol, 3.20 equiv) in anhydrous DCM (0.20 M, 8.70ml) at –78 °C (acetone/dry ice) under an N_2 atmosphere. The resulting mixture was stirred at –78 °C for 1 h. The reaction was warmed to ambient temperature, then heated to 45 °C (oil bath) for 4 h. The reaction was cooled to ambient temperature, filtered through celite washing with DCM and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, hexane:acetone 96:4) to yield tetra(boronic ester) **446** (952.4 mg, 80%, >95:5 *dr*) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05–5.47 (m, 2H, 2 x C*H*=CH_2), 4.97 (dd, *J* = 17.1, 2.2 Hz, 2H, 2 x CH=C*H*H), 4.88 (d, *J* = 10.1 Hz, 2H, 2 x CH=CH*H*), 2.25–1.96 (m, 4H,

C*H*$_2$CH=CH$_2$), 1.51–1.40 (m, 2H, CH$_2$), 1.39–1.27 (m, 4H, CH$_2$), 1.20 (s, 48H, 4 x pinacol-C*H*$_3$), 1.16–1.01 (m, 4H, C*H*-Bpin) ppm.

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.8 (CH), 114.5 (CH$_2$) 82.6 (pinacol-C), 82.4 (pinacol-C),35.7 (CH$_2$), 33.4 (CH$_2$), 32.8 (CH$_2$), 24.8 (pinacol-CH$_3$), 24.7 (pinacol-CH$_3$), 24.6 (pinacol-CH$_3$) ppm.
Carbon atom next to boron not observed due to quadrupolar relaxation.

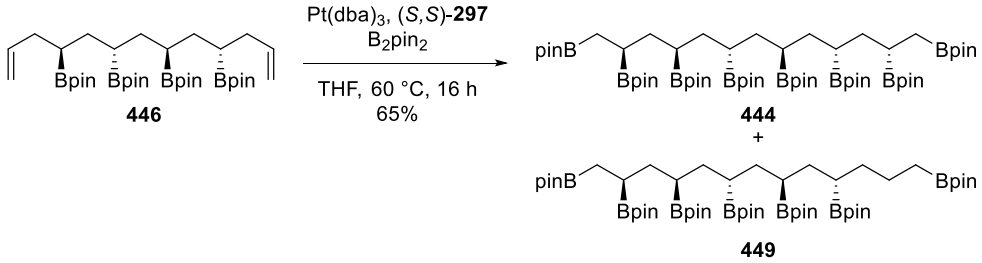
HRMS (ESI) calculated for $C_{37}H_{68}O_8Na$ $[M+Na]^+$ 707.5202, found 707.5214.

IR (ν_{max}/cm^{-1}, neat) 2977, 2915, 1378, 1370, 1306, 1141, 967, 862 and 670.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ (CHCl$_3$, *c* = 1.3) +7.2.

R$_f$ 0.23 (94:6 hexane:acetone).

2,2',2'',2''',2'''',2''''',2'''''',2'''''''-((2*S*,4*S*,6*R*,10*S*,12*S*)-Tridecan-1,2,4,6,8,10,12,13-octayl)octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**444**)



Pt(dba)$_3$ (19.8 mg, 0.011 mmol, 1.00 mol%), (*S*,*S*)-**297** (12.2 mg, 13.0 µmol, 1.20 mol%) and B$_2$pin$_2$ (599 mg, 2.36 mmol, 2.10 equiv) were dissolved in anhydrous THF (0.74 ml) before sealing the flask and heating to 80 °C (oil bath) for 30 min. After cooling to ambient temperature, tetra(boronic ester) **446** (767 mg, 1.12 mmol, 1.00 equiv) was added as a solution in anhydrous THF (0.37 ml) and the vessel was resealed and heated for 16 h at 60 °C (oil bath). The solution was then cooled to ambient temperature and concentrated *in vacuo*. The crude residue was directly purified by flash column chromatography (SiO$_2$, hexane:acetone 96:4) to yield octa(boronic ester) **444** (867.8 mg, 65%) as a white foam that was crushed into a fluffy white solid and diboration–hydroboration product **449** (83.6 mg, 7%) as a white foam that was crushed into a fluffy white solid.

444

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60–0.98 (m, 112H), 0.91 (dd, *J* = 15.9, 4.3 Hz, 2H, 2xBCH$_a$*H*$_b$), 0.72 (dd, *J* = 15.9, 11.0 Hz, 2H, 2 x BC*H*$_a$H$_b$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 82.7 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 36.1 (CH_2), 35.2 (CH_2), 35.1 (CH_2), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3),.25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3) ppm.
Carbon atom attached to boron not observed due to quadrupolar relaxation.

HRMS (MALDI) calculated for $C_{61}H_{116}B_8NaO_{16}$ $[M+Na]^+$ 1214.3971, found 1214.3968.

IR (ν_{max}/cm^{-1}, neat) 2978 2927, 1370, 1306, 1140, 968, 863, 848 and 672.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ ($CHCl_3$, *c* = 1) +0.98.

R*f* 0.17 (92:8 hexane:acetone).

449

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60–0.70 (m, 105H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 82.9 (pinacol-C), 82.8 (pinacol-C), 82.7 (pinacol-C), 82.7 (pinacol-C), 82.7 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 35.8 (CH_2), 35.4 (CH_2), 35.3 (CH_2), 35.2 (CH_2), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.8 (pinacol-CH_3) ppm.

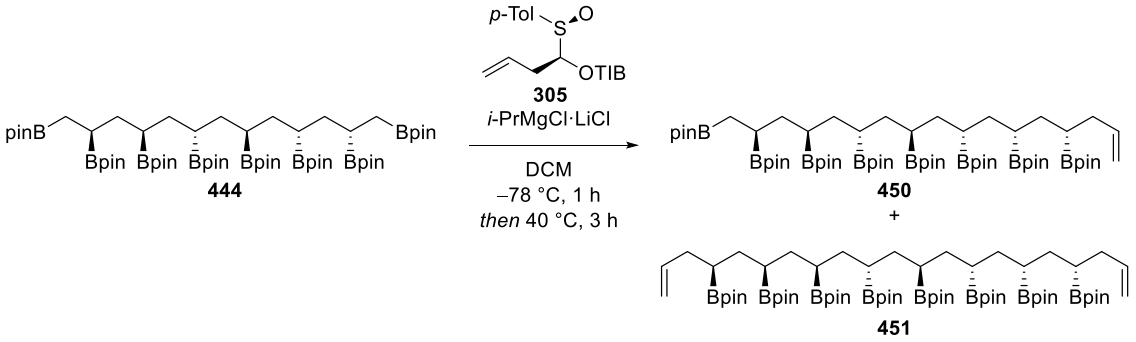
HRMS (MALDI) calculated for $C_{55}H_{105}B_7NaO_{14}$[*M*+Na]$^+$ 1088.8112, found 1088.8125.

IR (ν_{max}/cm^{-1}, neat) 2976.4, 2928.5, 1369.9, 1307.6, and 1141.1.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ ($CHCl_3$, *c* = 1) –14.

R*f* 0.21 (90:10 hexane:acetone).

2,2',2'',2''',2'''',2''''',2''''''-((2*S*,4*S*,6*R*,8*S*,10*R*,12*R*,14*R*)-Heptadec-16-en-1,2,4,6,8,10,12,14-octayl)octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**450**)



Octaboronic ester **444** (20.0 mg, 17.0 µmol, 1.00 equiv) and homoallylic sulfoxide **305** (19.6 mg, 42.5 µmol, 2.50 equiv) were charged to a flame dried Schlenk tube under N_2, which was put under high vacuum and stirred for 15 min. The Schlenk tube was backfilled with N_2 and anhydrous DCM (0.2 M, 0.09 ml) was added. The resulting mixture was cooled to –78 °C (acetone/dry ice) and *i*-PrMgCl·LiCl (0.04 ml, 44.2 µmol, 2.60 equiv) was added dropwise. The resulting reaction mixture was stirred at –78 °C for 1 h and was then warmed to 40 °C and stirred at this temperature for 3 h. The reaction was cooled to ambient temperature and the solvent removed under high vacuum. The crude residue was directly purified by column chromatography (SiO_2, hexane:acetone 96:4) to yield desymmetrised octaboronic ester **450** (9.9 mg, 47%) as a white foam and over homologated octaboronic ester **451** (6.0 mg, 27%) as a white foam.

450

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, alkene-C*H*), 5.00 (m, 1H, alkene-CH_aH_b), 4.87 (m, 1H, alkene-CH_aH_b), 2.26–2.18 (m, 1H, alkene-$CH_2CHCH_aH_b$), 2.11–2.02 (m, 1H, alkene-$CH_2CHCH_aH_b$), 1.55–0.79 (m, 117H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1 (CH), 114.6 (CH_2), 82.8 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 35.5 (CH_2), 34.9 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 31.1 (CH_2), 29.9 (CH_2), 27.3 (CH_2), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

HRMS (MALDI) calculated for $C_{65}H_{122}NaO_{16}B_8$ $[M+Na]^+$ 1268.9442, found 1268.9454.

IR (ν_{max}/cm^{-1}, neat) 2992.6, 2912.1, 1377.7, 1144.12 and 1067.2.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CHCl_3$, *c* = 0.1) –2.

R*f* 0.4 (92:8 hexane:acetone).

451

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 2H, 2 x alkene-C*H*), 5.00 (d, *J* = 17.1 Hz, 2H, 2 x alkene-C*H*$_a$H$_b$), 4.88 (d, *J* = 10.1 Hz, 2H, 2 x alkene-CH$_a$*H*$_b$), 2.26–2.18 (m, 2H, 2 x alkene-CH$_2$CHC*H*$_a$H$_b$), 2.11–2.02 (m, 2H, 2 x alkene-CH$_2$CHCH$_a$*H*$_b$), 1.55 – 0.79 (m, 118H) ppm.

^{13}C NMR (126 MHz, CDl_3) δ 139.1 (CH), 114.6 (CH_2), 82.8 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 35.5 (CH_2), 34.9 (CH_2), 34.6 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 31.0 (CH_2), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3) , 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

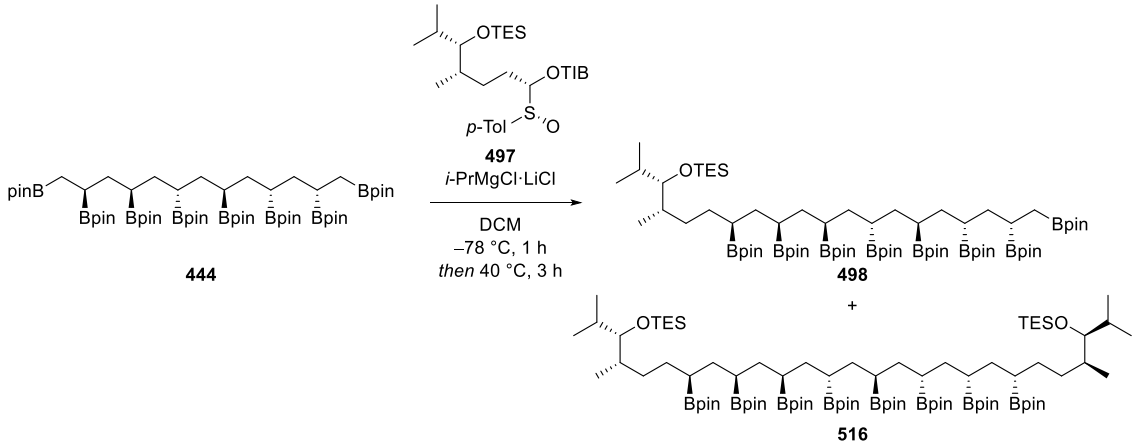
HRMS (MALDI) calculated for $C_{69}H_{128}B_8NaO_{16}$ $[M+Na]^+$ 1322.9913, found 1322.9926.

IR (ν_{max}/cm^{-1}, neat) 2977.3, 1375.3, 1307.7 and 1142.6.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ ($CHCl_3$, *c* = 0.1) –2.

R$_f$ 0.45 (8:92 acetone:hexane).

(((3*S*,4*S*,7*S*,9*S*,11S,13*S*,15*R*,17*S*,19*S*)-2,4-Dimethyl-7,9,11,13,15,17,19,20-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)icosan-3-yl)oxy)triethylsilane (**500**)



Octaboronic ester **444** (101 mg, 8.40 µmol, 1.00 equiv) and sulfoxide **497** (109 mg, 0.169 mmol, 2.00 equiv) were charged to a flame dried Schlenk tube under N_2, which was put under high vacuum and stirred for 15 min. The Schlenk tube was backfilled with N_2 and anhydrous DCM (0.20 M, 0.42 ml) was added. The resulting mixture was cooled to –78 °C (acetone/dry ice) and *i*-PrMgCl·LiCl (0.16 ml, 0.18 mmol, 2.10 equiv) was added dropwise. The resulting reaction mixture was stirred at –78 °C for 1 h and was then warmed to 40 °C and stirred at this temperature for 3 h. The reaction was cooled to ambient temperature and the solvent removed *in vacuo*. The crude residue was directly purified by flash column chromatography (SiO_2, hexane:acetone 96:4) to yield desymmetrised octaboronic ester **498** (44 mg, 48%) as a colourless oil and over homologated octaboronic ester **516** (40.7 mg, 28%) as a colourless oil.

498

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.17 (*app* t, *J* = 5.0 Hz, 1H, OC*H*), 1.72 (m, 1H, OCHC*H*), 1.58–0.99 (m, 140H), 0.94 (t, *J* = 7.9 Hz, 9H, Si($CH_2C\mathit{H}_3$)$_3$), 0.85–0.80 (m, 9H, OCHCH($C\mathit{H}_3$)$_2$) and CHCH_3), 0.70 (dd, *J* = 15.9, 11.0 Hz, 1H, BCH_aH$_b$), 0.59 (q, *J* = 7.9 Hz, 6H, Si($C\mathit{H}_2CH_3$)$_3$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 82.7 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.4 (CH), 36.9 (CH), 35.5 (CH_2), 35.3 (CH_2), 35.1 (CH_2), 34.9 (CH_2), 34.7 (CH_2), 34.0 (CH_2), 32.1 (CH_2), 31.5 (CH), 30.5 (CH), 28.4 (CH_2), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3),

24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3), 20.5 (CH_3), 18.3 (CH_3), 14.6 (CH_3), 7.4 (CH_3), 5.8 (CH_2) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

HRMS (MALDI) calculated for $C_{76}H_{148}NaO_{17}B_8Si$ $[M+Na]^+$ 1471.1201, found 1471.1218.

IR (ν_{max}/cm^{-1}, neat) 2976.5, 1370.3, 1306.6, and 1141.1.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ ($CHCl_3$, *c* = 1) –11.

R*f* 0.36 (90:10 hexane:acetone).

516

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (t, *J* = 5.0 Hz, 2H, 2 x OC*H*), 1.73 (m, 6H), 1.55–1.00 (m, 124H), 0.95 (t, *J* = 7.9 Hz, 18H, 2 x Si(CH_2CH_3)$_3$), 0.86–0.80 (m, 18H, OCHCH(CH_3)$_2$) and CHCH_3), 0.60 (q, *J* = 7.9 Hz, 12H, 2 x Si(CH_2CH_3)$_3$) ppm.

^{13}C NMR (126 MHz, CDl_3) δ 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.4 (pinacol-C), 82.4 (CH), 36.9 (CH), 35.0 (CH_2), 34.7 (CH_2), 34.1 (CH_2), 32.2 (CH_2), 31.6 (CH), 29.9 (CH_2), 28.5 (CH_2), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3), 20.5 (CH_3), 18.3 (CH_3), 14.7 (CH_3), 7.4 (CH_3), 5.8 (CH_2) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

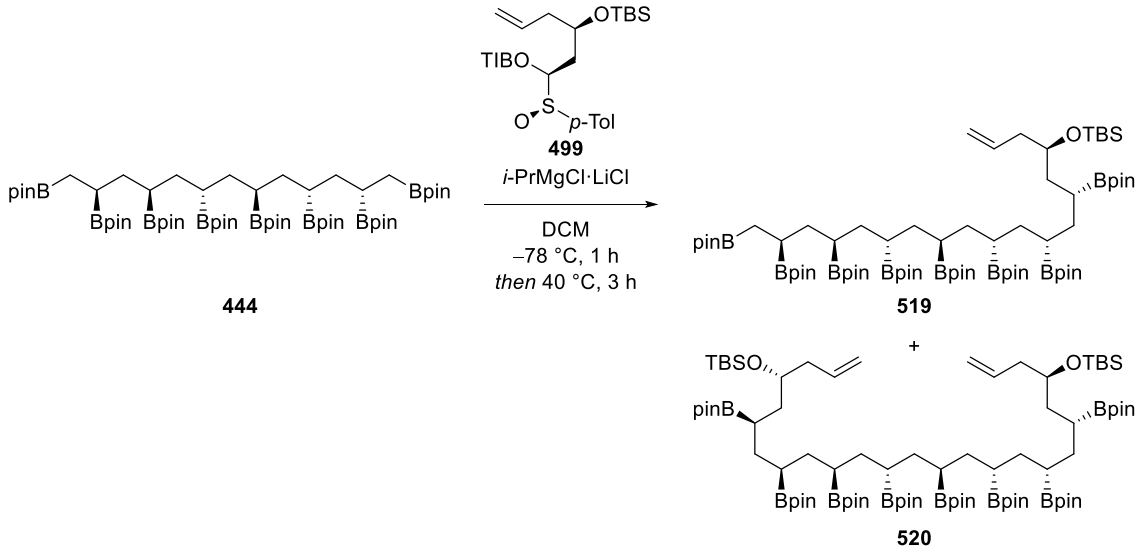
HRMS (MALDI) calculated for $C_{91}H_{180}NaO_{18}B_8Si_2$ $[M+Na]^+$ 1728.3421, found 1728.3436.

IR (ν_{max}/cm^{-1}, neat) 2974.9, 1459.0, 1377.9, 1307.1 and 1141.9.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ ($CHCl_3$, *c* = 0.1) –7.

R*f* 0.37 (90:10 hexane:acetone).

t-Butyldimethyl(((4*S*,6*R*,8*R*,10*R*,12*S*,14*R*,16*S*,18*S*)-6,8,10,12,14,16,18,19-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonadec-1-en-4-yl)oxy)silane (**519**)



Octaboronic ester **444** (47.7 mg, 4.00 µmol, 1.00 equiv) and sulfoxide **499** (59.9 mg, 0.10 mmol, 2.50 equiv) were charged to a flame dried Schlenk tube under N_2, which was put under high vacuum and stirred for 15 min. The Schlenk tube was backfilled with N_2 and anhydrous DCM (0.2 M, 0.2 ml) was added. The resulting mixture was cooled to –78 °C (acetone/dry ice) and *i*-PrMgCl·LiCl (0.09 ml, 0.104 mmol, 2.60 equiv) was added dropwise. The resulting reaction mixture was stirred at –78 °C for 1 h and was then warmed to 40 °C and stirred at this temperature for 3 h. The reaction was cooled to ambient temperature and the solvent removed under high vacuum. The crude residue was purified using a Biotage Isolera one system (loading method: dry load (~500 mg Telos), Snap Ultra 25g, 0% to 15% acetone in hexane, 15 column volumes) to give the title compound (**519**) (23 mg, 41%) as a white foam and over homologated octaboronic ester **520** (13.1 mg, 20%) as a white foam.

519

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H, alkene-C*H*), 5.06–4.97 (m, 2H, alkene CH_2), 3.68 (m, 1H, TBSOC*H*), 2.19 (m, 2H, alkene-CHCH_2), 1.61–0.90 (m, 117H), 0.94 (dd, *J* = 16.0, 4.3 Hz, 1H, BCH_aH_b) 0.89 (s, 9H, SiC(CH_3)$_3$), 0.73 (dd, *J* = 16.0, 11.1 Hz, 1H, BCH$_a$$H_b$), 0.08 (s, 3H, SiC$H_3$), 0.05 (s, 3H, SiC$H_3$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1 (CH), 116.3 (CH_2), 82.7 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 72.6 (CH), 42.9 (CH_2), 38.5

(CH_2), 35.6 (CH_2), 35.3 (CH_2), 35.2 (CH_2), 34.9 (CH_2), 33.7 (CH_2), 32.5 (CH_2), 26.2 (CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3), 18.3 (C), –4.0 (CH_3), –4.3 (CH_3) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

HRMS (MALDI) calculated for $C_{73}H_{140}NaO_{17}B_8Si$ $[M+Na]^+$ 1427.0573, found 1427.0585.

IR (ν_{max}/cm^{-1}, neat) 2976.7, 1370.1, 1306.1, and 1141.3.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CHCl_3$, *c* = 0.1) +1.

R*f* 0.31 (90:10 hexane:acetone).

520

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 2H, 2 x alkene-C*H*), 5.03–4.95 (m, 4H, 2 x alkene CH_2), 3.75–3.63 (m, 2H, 2 x TBSOC*H*), 2.30–2.12 (m, 4H, 2 x alkene-CHCH_2), 1.56–0.95 (m, 122H), 0.86 (s, 18H, 2 x SiC(CH_3)$_2$), 0.06 (s, 6H, 2 x SiCH_3), 0.03 (s, 6H, 2 x SiCH_3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1 (CH), 116.3 (CH_2), 82.7 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 72.6 (CH), 42.9 (CH_2), 38.5 (CH_2), 35.0 (CH_2), 33.8 (CH_2), 32.5 (CH_2), 26.2 (CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1(pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 18.3 (C), –4.0 (CH_3), –4.3 (CH_3) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

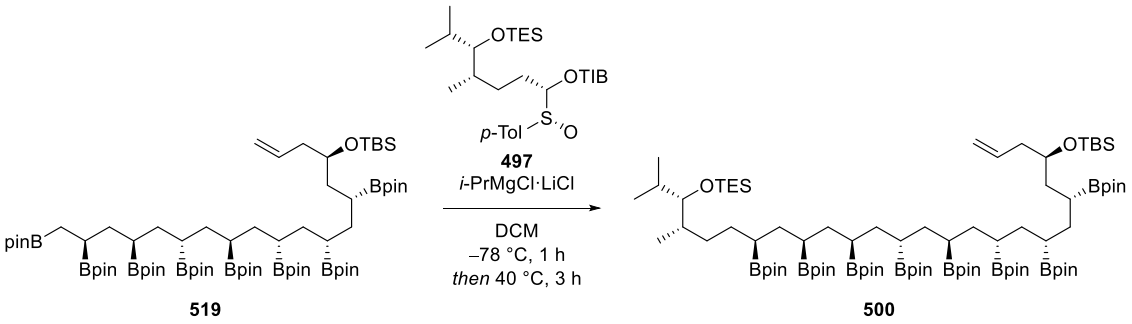
HRMS (MALDI) calculated for $C_{85}H_{164}$ $B_8NaO_{18}Si_2$ $[M+Na]^+$ 1640.2166, found 1640.2185.

IR (ν_{max}/cm^{-1}, neat) 2976.5, 2927.9, 1378.2 1306.6 and 1142.1.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CHCl_3$, *c* = 1) +24.

R*f* 0.33 (92:8 hexane:acetone).

(5*S*,7*R*,9*R*,11*R*,13*S*,15*R*,17*S*,19*S*,21*S*,24*S*,25*S*)-5-Allyl-27,27-diethyl-25-isopropyl-2,2,3,3,24-pentamethyl-7,9,11,13,15,17,19,21-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,26-dioxa-3,27-disilanonacosane (**500**)



Octaboronic ester **519** (50.0 mg, 36.5 µmol, 1.00 equiv) and sulfoxide **497** (115 mg, 0.178 mmol, 5.00 equiv) were charged to a flame dried Schlenk tube under N_2, which was put under high vacuum and stirred for 15 min. The Schlenk tube was backfilled with N_2 and anhydrous DCM (0.20 M, 0.18 ml) was added. The resulting mixture was cooled to –78 °C (acetone/dry ice) and *i*-PrMgCl·LiCl (0.16 ml, 0.18 mmol, 5.1 equiv) was added dropwise. The resulting reaction mixture was stirred at –78 °C for 1 h and was then warmed to 40 °C and stirred at this temperature for 3 h. The reaction was cooled to ambient temperature and the solvent removed under high vacuum. The crude residue was purified using a Biotage Isolera one system (loading method: dry load (~500 mg Telos), Sfär Silica HC D 25g, 0% to 15% acetone in hexane, 15 column volumes) to give the title compound (**500**) (43.3 mg, 72%) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1H, alkene-C*H*), 5.03–4.95 (m, 2H, alkene-CH_2), 3.66 (m, 1H, TBSOC*H*), 3.18 (*app* t, *J* = 5.0 Hz, 1H, TESOC*H*), 2.17 (m, 2H, CH_2=CHCH_2), 1.73 (m, 2H), 1.54–1.00 (m, 124H), 0.95 (t, *J* = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 0.88–0.81 (m, 18H, TESOCHCH(CH_3)$_2$) and CHCH_3 and SiC(CH_3)$_3$), 0.60 (q, *J* = 7.9 Hz, 6H, Si(CH_2CH_3)$_3$), 0.06 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.1 (CH), 116.3 (CH_2), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.4 (CH), 72.6 (CH), 42.9 (CH_2), 38.5 (CH_2), 36.9 (CH), 35.8 (CH_2), 34.7 (CH_2), 34.1 (CH_2), 33.8 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 31.6 (CH), 26.2 (CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 20.5 (CH_3), 18.3 (CH_3), 18.3 (C), 14.7 (CH_3), 7.4 (CH_3), 5.8 (CH_2), –4.0 (CH_3), –4.3 (CH_3) ppm.

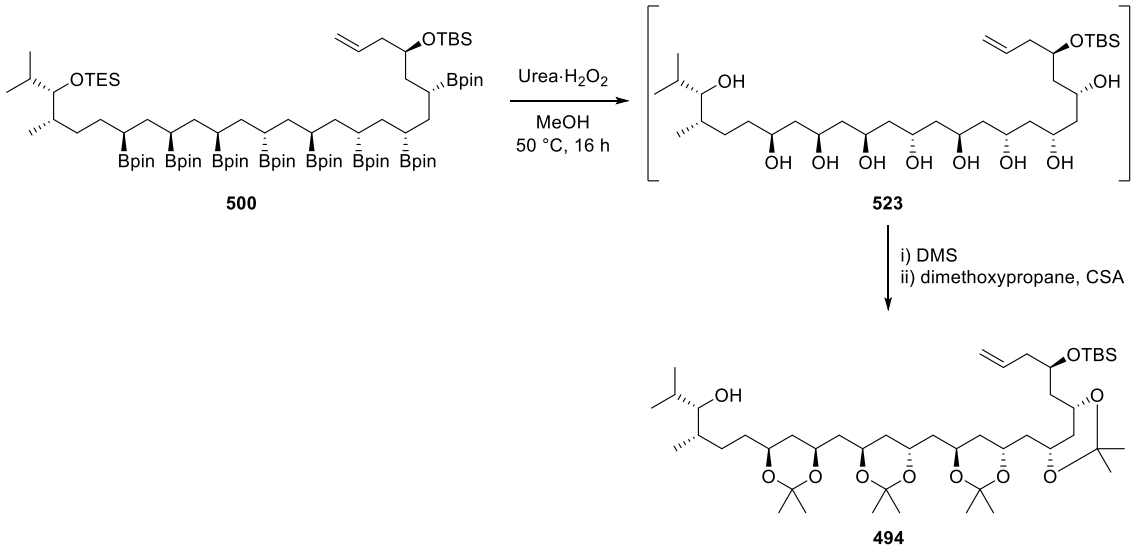
HRMS (MALDI) calculated for $C_{88}H_{172}B_8NaO_{18}Si_2$ $[M+Na]^+$ 1684.2793, found 1684.2780.

IR (ν_{max}/cm^{-1}, neat) 2975.4, 1378.2 1306.5 and 1141.8.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ ($CHCl_3$, *c* = 0.1) +12.

$\mathbf{R}_f$ 0.34 (92:8 hexane:acetone).

(3*S*,4S)-6-((4*S*,6*S*)-6-(((4*R*,6*R*)-6-(((4*R*,6*R*)-6-(((6*S*)-6-((*R*)-2-((*t*-Butyldimethylsilyl)oxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2,4-dimethylhexan-3-ol (**494**)



Urea·H_2O_2 complex (900 mg, 15.0 mmol, 60.0 equiv) was added to a stirred solution of **500** (421.4 mg, 0.25 mmol, 1.00 equiv) in anhydrous MeOH (0.10 M, 2.50 ml). The resulting reaction mixture was stirred at 50 °C for 16 h. The reaction mixture was then cooled to 0 °C and DMS (2.20 ml, 30.0 mmol, 120 equiv) was added, after which the reaction mixture was warmed to ambient temperature and stirred for 10 min before the volatiles were removed *in vacuo*. The crude nonol **523** was diluted with dimethoxypropane (3.00 ml, 24.4 mmol, 97.6 equiv), and CSA (11.6 mg, 0.005 mmol, 20 mol%) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. TLC analysis showed many spots, which were presumably differing levels of acetonide protection. The reaction mixture was then filtered through a small pad of sand washing with EtOAc and concentrated *in vacuo*. The residue was diluted with dimethoxypropane (3.00 ml, 24.4 mmol, 97.6 equiv), and CSA (11.6 mg, 0.005 mmol, 20

mol%) was added. The resulting reaction mixture was stirred at ambient temperature for a further 3 h, after which TLC analysis showed a single product spot. The reaction mixture was concentrated *in vacuo* and the crude residue purified by column chromatography (SiO_2, pentane:Et_2O 70:30) to yield **494** (120 mg 58%, >95:5 *dr*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 18.5, 8.7, 7.1 Hz, 1H, alkene-C*H*), 5.06–4.99 (m, 2H, alkene-CH_2), 4.02–3.91 (m, 8H, 8 x acetonideOC*H*), 3.81–3.75 (m, 1H, TBSOC*H*), 1.30 (dd, *J* = 7.7, 3.9 Hz, 1H, HOC*H*), 2.29–2.16 (m, 2H, CH_2=CHCH_2), 1.86–1.77 (m, 2H, CH_2), 1.75–1.66 (m, 2H, CH_2), 1.65–1.39 (m, 16H), 1.36 (s, 3H, *syn*-acetonide CH_3), 1.34 (s, 3H, *syn*-acetonide CH_3), 1.32 (s, 12H, 4 x *anti*-acetonide CH_3), 1.25 (s, 3H, *syn*-acetonide CH_3), 1.23 (s, 3H, *syn*-acetonide CH_3), 1.16 (m, 2H, CH_2), 0.96 (d, *J* = 6.6 Hz, 3H, HOCHCHCH_3), 0.90–0.84 (m, 15H, OCHCH(CH_3)$_2$) and SiC(CH_3)$_3$), 0.07 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.8 (CH), 117.2 (CH_2), 100.5 (*anti*-acetonide C), 100.4 (*anti*-acetonide C), 98.5 (*syn*-acetonide C), 98.5 (*syn*-acetonide C), 80.0 (CH), 69.2 (CH), 67.8 (CH), 65.8 (CH), 65.6 (CH), 65.6 (CH), 63.1 (CH), 62.8 (CH), 44.4 (CH_2), 42.8 (CH_2), 42.6 (CH_2), 42.5 (CH_2), 42.2 (CH_2), 38.9 (CH_2), 37.6 (CH_2), 36.8 (CH_2), 35.0 (CH), 34.1 (CH_2), 31.7 (CH_2), 31.1 (CH), 30.5 (*syn*-acetonide CH_3), 30.4 (*syn*-acetonide CH_3), 29.3 (CH_2), 26.1 (CH_3), 25.0 (*anti*-acetonide CH_3), 24.9 (*anti*-acetonide CH_3), 22.8 (CH_2), 20.4 (*syn*-acetonide CH_3), 20.0 (*syn*-acetonide CH_3), 19.5 (CH_3), 18.7 (CH_3), 18.3 (C), 14.3 (CH_3), 13.2 (CH_3), 1.17 (CH_3), –3.8 (CH_3), –4.3 (CH_3) ppm.

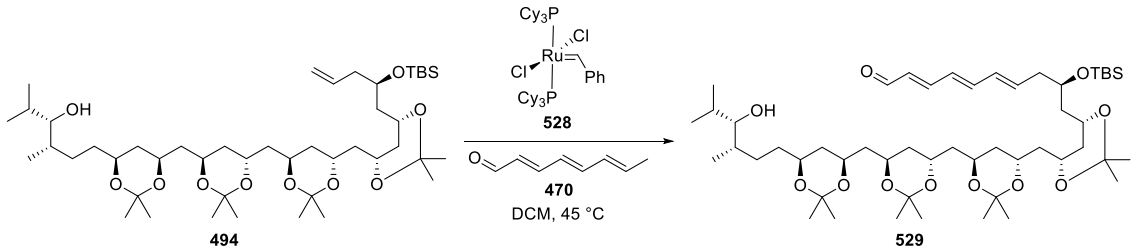
HRMS (MALDI) calculated for $C_{46}H_{86}NaO_{10}Si$ $[M+Na]^+$ 849.5882, found 849.5889.

IR (ν_{max}/cm^{-1}, neat) 3500.0 (br), 2958.7, 2928.2, 2870.4, 1461.7 and 1251.3.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$($CHCl_3$, *c* = 0.37) –3.

R*f* 0.8 (1:1 pentane:Et_2O).

(2*E*,4*E*,6*E*,9*R*)-9-((*t*-Butyldimethylsilyl)oxy)-10-((4*S*)-6-(((4*R*,6*R*)-6-(((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((3*S*,4*S*)-4-hydroxy-3,5-dimethylhexyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)deca-2,4,6-trienal (**529**)



According to a modified literature procedure,[125] Grubbs first generation metathesis catalyst (**528**) (3.00 mg, 0.0037 mmol, 10.0 mol%) was added to a stirred solution of poly(acetonide) **494** (30.8 mg, 0.037 mmol, 1.00 equiv) and trienal **470** (45.5 mg, 0.37 mmol, 10.0 equiv) in anhydrous DCM (0.025 M, 1.48 ml) under an atmosphere of N_2. The resulting mixture was stirred at 45 °C (sand bath) for 6 h, at which point TLC analysis showed incomplete consumption of **494**. A further portion of Grubbs first generation catalyst (**528**) (3.00 mg, 0.0037 mmol, 10 mol%) was added and the reaction was stirred for a further 16 h at 45 °C. The reaction was cooled to ambient temperature and the volatile components were removed *in vacuo*. The crude residue was purified by column chromatography (SiO_2, pentane:Et_2O 1:1) to yield **529** (24.5 mg, 73%, 89% brsm) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (d, *J* = 7.8 Hz, 1H, C*H*O), 7.13–7.09 (m, 1H), 6.65 (dd, *J* = 14.9, 10.8 Hz, 1H), 6.33–6.30 (m, 1H), 6.23–6.20 (m, 1H), 6.18–6.11 (m, 2H), 4.02–3.92 (m, 8H, 8 x acetonideOC*H*), 3.83–3.75 (m, 1H, TBSOC*H*), 3.11 (m, 1H, HOC*H*), 2.34–2.28 (m, 2H, CH_2=CHCH_2), 1.86–1.77 (m, 2H, CH_2), 1.75–1.66 (m, 2H, CH_2), 1.65–1.39 (m, 16H), 1.36 (s, 3H, *syn*-acetonide CH_3), 1.34 (s, 3H, *syn*-acetonide CH_3), 1.32 (s, 12H, 4 x *anti*-acetonide CH_3), 1.25 (s, 3H, *syn*-acetonide CH_3), 1.23 (s, 3H, *syn*-acetonide CH_3), 1.16 (m, 2H, CH_2),), 0.96 (d, *J* = 6.6 Hz, 3H, HOCHCHCH_3), 0.90–0.84 (m, 15H, OCHCH(CH_3)$_2$) and SiC(CH_3)$_3$), 0.07 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2 (CH), 148.8 (CH), 143.0 (CH), 135.1 (CH), 132.2 (CH), 131.1 (CH), 130.5 (CH), 100.5 (*anti*-acetonide C), 98.5 (*syn*-acetonide C), 80.0 (CH), 69.2 (CH), 66.1 (CH), 65.8 (CH), 65.6 (CH), 63.1 (CH), 62.8 (CH), 44.8 (CH_2), 42.5 (CH_2), 42.2 (CH_2), 38.9 (CH_2), 36.8 (CH_2), 35.0 (CH), 34.2 (CH_2), 31.7 (CH_2), 31.1

(CH), 30.5 (*syn*-acetonide CH_3), 30.4 (*syn*-acetonide CH_3), 29.9 (CH_2), 26.0 (CH_3), 25.0 (*anti*-acetonide CH_3), 25.0 (*anti*-acetonide CH_3), 20.3 (*syn*-acetonide CH_3), 20.0 (*syn*-acetonide CH_3), 19.5 (CH_3), 18.8 (CH_3), 18.3 (C), 14.3 (CH_3), 13.2 (CH_3), 1.18 (CH_3), –3.8 (CH_3), –4.3 (CH_3) ppm.

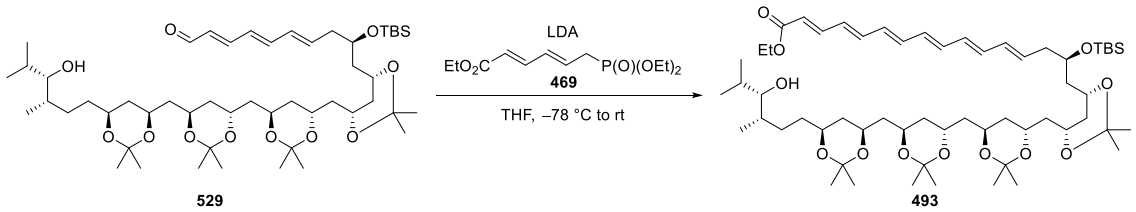
HRMS (MALDI) calculated for $C_{51}H_{90}NaO_{11}Si$ $[M+Na]^+$ 929.6145, found 929.6154.

IR (ν_{max}/cm^{-1}, neat) 3498.7, 2927.0, 1610.0, 1461.7 and 1224.9.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ ($CHCl_3$, *c* = 1) –3.

R*f* 0.23 (1:1 pentane:Et_2O).

Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,15*R*)-15-((*t*-butyldimethylsilyl)oxy)-16-((4*S*)-6-(((4*R*,6*R*)-6-(((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((3*S*,4*S*)-4-hydroxy-3,5-dimethylhexyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)hexadeca-2,4,6,8,10,12-hexaenoate (**493**)



According to a modified literature procedure,[125] *n*-BuLi (1.6 M in hexane, 30 µl, 0.049 mmol, 3.5 equiv) was added to a stirred solution of *i*-Pr_2NH (7.0 µl, 0.051 mmol, 3.7 equiv) in anhydrous THF (0.23 M, 0.22 ml) at –78 °C (acetone/dry ice) under an atmosphere of N_2. The resulting mixture was warmed to ambient temperature and stirred for 10 min, then cooled to –78 °C. A solution of phosphonate **469** (13.5 mg, 0.049 mmol, 3.50 equiv) in anhydrous THF (0.22 M, 0.22 ml) was added dropwise and the resulting mixture was stirred at –78 °C for 30 min. A solution of aldehyde **529** (12.6 mg, 0.014 mmol, 1.00 equiv) in anhydrous THF (0.38 M, 36 µl) was added dropwise and the resulting mixture stirred –78 °C for 30 min, and then at ambient temperature for 16 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1.00 ml) and was diluted with Et_2O (1.0 ml). The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 1.0 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, pentane:Et_2O 60:40) to yield the title compound (**493**) (10.4 mg, 72%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 15.2, 11.6 Hz, 1H, O=CCHC*H*), 6.60 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.47–6.41 (m, 1H), 6.39–6.24 (m, 6H), 6.22–6.07 (m, 2H), 5.86 (d, *J* = 15.2 Hz, 1H, O=CC*H*), 4.01–3.92 (m, 8H, 8 x acetonideOC*H*), 3.79 (m, 1H, TBSOC*H*), 3.11 (m, 1H, HOC*H*), 2.43–2.29 (m, 2H, CH_2=CHCH_2), 1.82 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.65–1.39 (m, 16H), 1.37 (s, 3H, *syn*-acetonide CH_3), 1.35 (s, 3H, *syn*-acetonide CH_3), 1.33 (s, 12H, 4 x *anti*-acetonide CH_3), 1.25 (s, 3H, *syn*-acetonide CH_3), 1.23 (s, 3H, *syn*-acetonide CH_3), 1.16 (m, 2H, CH_2), 0.96 (d, *J* = 6.6 Hz, 3H, HOCHCHCH_3), 0.90–0.84 (m, 15H, OCHCH(CH_3)$_2$) and SiC(CH_3)$_3$), 0.07 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3 (C=O), 144.6 (CH), 141.0 (CH), 137.5 (CH), 136.0 (CH), 135.0 (CH), 133.0 (CH), 132.7 (CH), 132.2 (CH), 131.7 (CH), 131.1 (CH), 129.9 (CH), 120.6 (CH), 100.4 (*anti*-acetonide C), 98.5 (*syn*-acetonide C) 80.0 (CH), 69.2 (CH), 68.1 (CH), 65.8 (CH), 65.6 (CH), 63.1 (CH), 63.1 (CH), 62.8 (CH) 44.7 (CH_2), 42.6 (CH_2), 42.4 (CH_2), 42.2 (CH_2), 38.9 (CH_2), 37.5 (CH_2), 36.8 (CH_2), 35.0 (CH), 34.2 (CH_2), 31.7 (CH_2), 31.1 (CH), 30.4 (*syn*-acetonide CH_3), 30.4 (*syn*-acetonide CH_3), 29.3 (CH_2), 26.1 (CH_3), 25.0 (*anti*-acetonide CH_3), 25.0 (*anti*-acetonide CH_3), 22.9 (CH_2), 20.4 (*syn*-acetonide CH_3), 20.0 (*syn*-acetonide CH_3), 19.5 (CH_3), 18.7 (CH_3), 18.3 (C), 14.5 (CH_3), 13.2 (CH_3), 1.18 (CH_3), –3.8 (CH_3), –4.3 (CH_3) ppm.

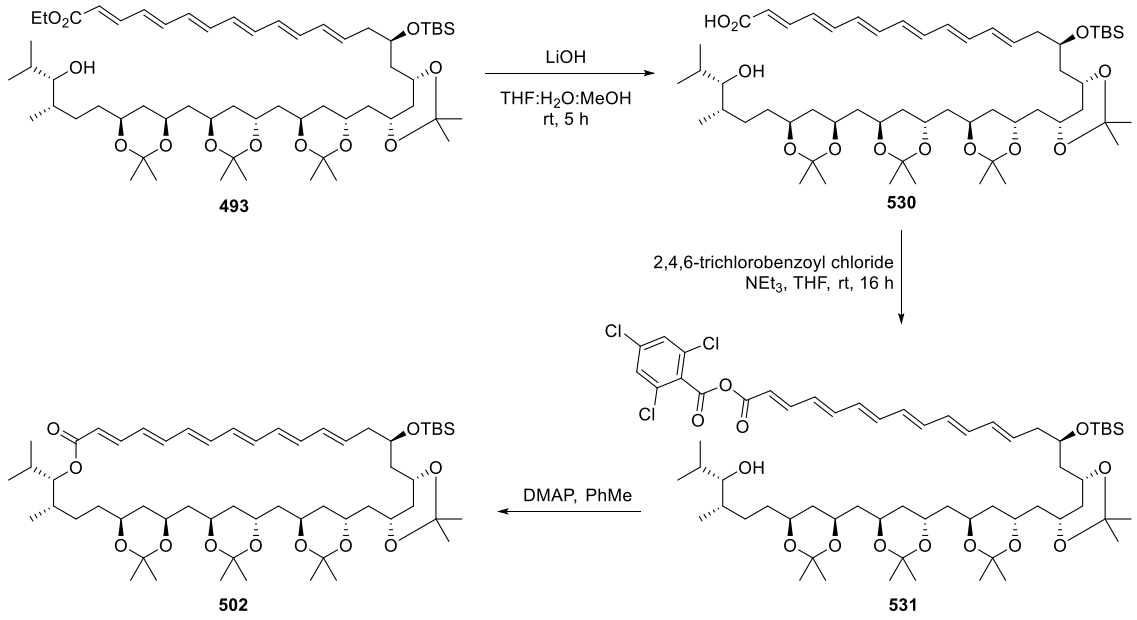
HRMS (MALDI) calculated for $C_{59}H_{100}NaO_{12}Si$ $[M+Na]^+$ 1051.6876, found 1051.6889.

IR (ν_{max}/cm^{-1}, neat) 3506.8, 2928.3, 1708.3, 1620.3 and 1562.8.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$($CHCl_3$, *c* = 2) –8.

R*f* 0.42 (1:1 pentane:Et_2O).

Protected bahamaolide A (**502**)



Ester saponification

$LiOH{\cdot}H_2O$ (13.0 mg, 0.31 mmol, 64.5 equiv) was added to a stirred solution of compound **493** (5.00 mg, 4.86 µmol, 1.00 equiv) in a mixture of THF:H_2O:MeOH (0.65 ml:0.16 ml:0.16 ml). The resulting mixture was stirred at ambient temperature for 5 h. The reaction was diluted with H_2O (0.50 ml) and EtOAc (0.50 ml) and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 0.50 ml) and the combined organics were dried over $MgSO_4$, filtered and concentrated. The crude residue was taken forward to the next step with no additional purification.

Formation of mixed anhydride **531**

NEt_3 (6.00 µl, 0.05 mmol, 10.3 equiv) and 2,4,6-trichlorobenzoyl chloride (5.00 µl, 0.03 mmol, 7.00 equiv) were added to a stirred solution of carboxylic acid **530** in anhydrous THF (0.0075 M, 0.65 ml) under an atmosphere of N_2. The resulting mixture was stirred at ambient temperature for 16 h before being filtered through a celite pad, which had been pre-washed with 5.0 ml of anhydrous THF. The mother liquor was concentrated and used directly in the next step with no additional purification.

Macrolactonisation

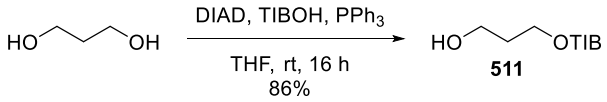
A solution of mixed anhydride **531** in anhydrous PhMe (0.002 M, 2.43 ml) was added to a stirred solution of DMAP (11.9 mg, 97.2 µmol, 20.0 equiv) in anhydrous PhMe

(0.009 M, 10.8 ml) via syringe pump over 6 h at ambient temperature under an atmosphere of N_2. After the addition was complete, the syringe was washed with 0.41 ml of anhydrous PhMe, which was also added to the reaction. The resulting mixture was stirred at ambient temperature for 16 h, after which the solvent was removed *in vacuo*. The crude residue was filtered through a pad of silica gel (hexane:EtOAc 8:1) and the mother liquor concentrated to afford protected bahamaolide A (**502**) (2.6 mg, 53%) as a yellow oil.

*Sammakia has shown that the corresponding intermediate in the synthesis of dermostatin A is not stable to purification and so **502** was characterised by HRMS only and then carried forward to the deprotection step.*

HRMS (MALDI) calculated for $C_{57}H_{94}NaO_{11}Si$ $[M+Na]^+$ 1005.6458 found 1005.6468.

3-Hydroxypropyl 2,4,6-triisopropylbenzoate (**511**)



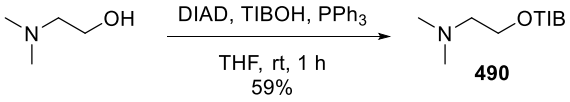
According to a modified literature procedure,[43] DIAD (4.87 ml, 24.7 mmol, 1.00 equiv.) was added dropwise to a stirred solution of propane-1,3-diol (5.35 ml, 74.1 mmol, 3.00 equiv.), triisopropylbenzoic acid (6.00 g, 27.2 mmol, 1.10 equiv.) and triphenylphosphine (7.13 mg, 27.2 mmol, 1.10 equiv.) in THF (0.70 M, 35 ml) at 0 °C (water/ice). The resulting reaction mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The crude residue was purified directly by column chromatography (SiO_2, petroleum ether:EtOAc 8:2), to afford the title compound (**511**) (6.51 g, 86%) as a colourless oil.

All data matched that reported in the literature.[207]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 2H, Ar*H*), 4.44 (t, *J* = 6.3 Hz, 2H, TIBOC*H*$_2$), 3.76 (t, *J* = 6.1 Hz, 2H, C*H*$_2$OH), 2.94–2.77 (m, 3H, 3xArC*H*), 2.02–1.93 (m, 2H, C*H*$_2$CH$_2$OH), 1.23 (d, *J* = 6.9 Hz, 18H, 6 x C*H*$_3$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (C), 150.3 (C), 144.8 (C), 130.4 (C), 121.0 (CH), 62.1, (CH) 59.5 (CH), 34.5 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 24.2 (CH_3), 24.0 (CH_3) ppm.

2-(Dimethylamino)ethyl 2,4,6-triisopropylbenzoate (**490**)



According to a modified literature procedure,[43] DIAD (1.21 ml, 6.17 mmol, 1.10 equiv.) was added dropwise to a stirred solution of 2-(dimethylamino)ethan-1-ol (0.56 ml, 5.61 mmol, 1.00 equiv.), 2,4,6-triisopropylbenzoic acid (1602 mg, 6.45 mmol, 1.15 equiv.) and triphenylphosphine (1618 mg, 6.17 mmol, 1.10 equiv.) in THF (0.66 M, 8.5 ml) at 0 °C (water/ice). The resulting reaction mixture was stirred at ambient temperature for 1 h before being concentrated *in vacuo*. The crude residue was purified directly by column chromatography (SiO_2, pentane:Et_2O 2:8), to afford the title compound (**490**) (1049 mg, 59%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 2H, Ar*H*), 4.42 (t, *J* = 6.1 Hz, 2H, OCH_2), 2.94–2.83 (m, 3H, 3 x ArC*H*), 2.67 (t, *J* = 6.1 Hz, 2H, NCH_2), 2.31 (s, 6H, N(CH_3)$_2$), 1.24 (d, *J* = 6.8 Hz, 12H, 2 x *o*ArC(CH_3)$_2$), 1.24 (d, *J* = 6.9 Hz, 6H, *p*ArC(CH_3)$_2$) ppm.

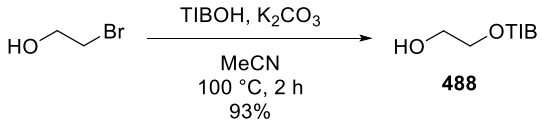
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C=O), 150.1 (C), 144.8 (C), 130.4 (C), 120.8 (CH), 62.4 (CH_2), 57.6 (CH_2), 45.5 (CH_3), 34.4 (CH), 31.5 (CH), 24.2 (CH_3), 24.0 (CH_3) ppm.

HRMS (ESI) calculated for $C_{20}H_{33}NO_2$ $[M+H]^+$ 320.2584, found 320.2583.

IR (ν_{max}/cm^{-1}, neat) 2957.72, 2768.63, 1724.61, 1605.1, 1451.29 and 1248.85.

R_f 0.28 (7:3 Et_2O:pentane).

2-Hydroxyethyl 2,4,6-triisopropylbenzoate (**488**)



According to a modified literature procedure,[204] a suspension of 2,4,6-triisopropylbenzoic acid (500 mg, 2.01 mmol, 1.00 equiv) and K_2CO_3 (556 mg, 4.02 mmol, 2.00 equiv.) in MeCN (0.33 M, 6.1 ml) was stirred vigorously for 15 min. 2-Bromoethanol (0.28 ml, 4.0 mmol, 2.0 equiv) was added and the resulting suspension heated at 100 °C (oil bath) for 2 h. The reaction mixture was cooled to ambient temperature, filtered through celite (EtOAc) and concentrated *in vacuo* to a yellow oil. The crude residue was purified by

column chromatography (SiO_2, pentane:Et_2O 70:30) to afford **488** (546.2 mg, 93%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H, Ar*H*), 4.44 (m, 2H, TIBOCH_2), 3.92 (m, 2H, HOCH_2), 2.95–2.81 (m, 3H, 3 x ArC*H*), 1.87 (t, *J* = 6.2 Hz, 1H, O*H*), 1.26 (d, *J* = 6.8 Hz, 12H, 2 x *o*ArC(CH_3)$_2$), 1.25 (d, *J* = 6.9 Hz, 6H, *p*ArC(CH_3)$_2$) ppm.

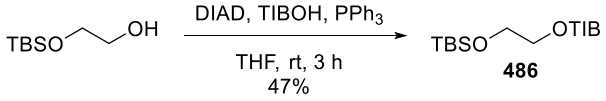
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.4 (C), 144.8 (C), 130.0 (C), 120.9 (CH), 66.5 (CH_2), 61.3 (CH_2), 34.5 (CH), 31.6 (CH), 24.2 (CH_3), 24.0 (CH_3) ppm.

HRMS (ESI) calculated for $C_{18}H_{29}O_3$ $[M+H]^+$ 293.2111, found 293.2116.

IR (ν_{max}/cm^{-1}, neat). 3438.74 (br), 2960.1, 2870.2, 1725.8, 1650.9 and 1460.5.

R_f 0.23 (70:30 pentane:Et_2O).

2-((*t*-Butyldimethylsilyl)oxy)ethyl 2,4,6-triisopropylbenzoate (**486**)



According to a modified literature procedure,[43] DIAD (0.64 ml, 3.24 mmol, 1.10 equiv) was added dropwise to a stirred solution of 2-((*t*-butyldimethylsilyl)oxy)ethan-1-ol (520 mg, 2.95 mmol, 1.00 equiv), 2,4,6-triisopropylbenzoic acid (842 mg, 3.39 mmol, 1.15 equiv) and triphenylphosphine (850 mg, 3.24 mmol, 1.10 equiv) in THF (0.66 M, 4.5 ml) at 0 °C (water/ice). The resulting reaction mixture was stirred at ambient temperature for 3 hr before being concentrated *in vacuo*. The crude residue was purified directly by column chromatography (SiO_2, pentane:Et_2O 90:10), to afford **486** (560 mg, 47%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, Ar*H*), 4.36 (m, 2H, OCH_2), 3.90 (m, 2H, OCH_2), 2.94–2.83 (m, 3H, 3 x ArC*H*), 1.24 (d, *J* = 7.0 Hz, 6H, *p*ArC(CH_3)$_2$), 1.24 (d, *J* = 6.9 Hz, 12H, 2 x *o*ArC(CH_3)$_2$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 6H, Si(CH_3)$_2$) ppm.

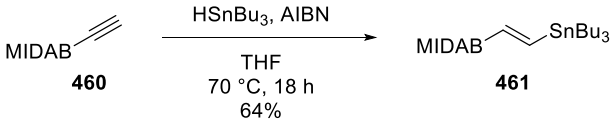
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.2 (C), 145.0 (C), 130.6 (C), 121.0 (CH), 66.4 (CH_2), 61.3 (CH_2), 34.6 (CH), 31.6 (CH), 26.0 (CH_3), 24.3 (CH_3), 24.1 (CH_3), 18.4 (CH_3), –5.2 (C) ppm.

HRMS (ESI) calculated for $C_{24}H_{42}NaO_3Si$ $[M+Na]^+$ 429.2795, found 429.2804.

IR (ν_{max}/cm^{-1}, neat). 2958.7, 2929.2, 2868.8, 1726.5, 1461.8 and 1250.6.

$\mathbf{R}_f$ 0.8 (90:10 pentane:Et_2O).

(*E*)-6-Methyl-2-(2-(tributylstannyl)vinyl)-1,3,6,2-dioxazaborocane-4,8-dione (**461**)



According to a literature procedure,[208] tributyltin hydride (0.45 ml, 1.66 mmol, 1.50 equiv) was added to a stirred solution of 2-ethynl-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (**460**) (200 mg, 1.11 mmol, 1.00 equiv) and AIBN (18 mg, 0.11 mmol. 0.10 equiv) in THF (0.20 M, 5.6 ml). The resulting reaction mixture was heated at 70 °C for 18 h before being cooled to ambient temperature and successively washed with a 1 M aqueous solution of HCl (10 ml), a saturated aqueous solution of $NaHCO_3$ (10 ml) and brine (10 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, Et_2O to Et_2O:MeCN 5:1) to afford the title compound (**461**) (336 mg, 64%, *E*/*Z* >95:5) as a white solid.

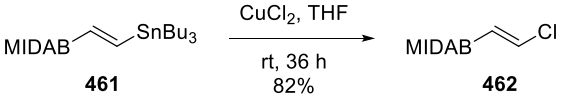
All spectral data matched that reported in the literature.[208]

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.80 (d, *J* = 21.7 Hz and dd, 122.7, 2.2 Hz and dd, 79.6, 2.2 Hz, 1H, C*H*), 6.29 (d, *J* = 21.7 Hz and dd, *J* = 113.3, 2.1 Hz dd, *J* = 69.9, 2.1 Hz, 1H, C*H*), 4.20 (d, *J* = 17.0 Hz, 2H, NCH_2), 3.98 (d, *J* = 17.0 Hz, 2H, NCH_2), 2.74 (s, 3H, NCH_3), 1.54–1.43 (m, 6H, 3 x $SnCH_2CH_2$), 1.33–1.23 (m, 6H, 3 x $SnCH_2CH_2CH_2$), 0.91–0.82 (m, 15H, 3 x $SnCH_2$ and 3 x $SnCH_2CH_2CH_2CH_3$) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ 169.2 (C=O), 145.6 (CH), 61.5 (CH_2), 46.8 (CH_3), 28.6 (CH_2), 26.6 CH_2), 13.6 (CH_2), 9.0 (CH_3) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

(*E*)-2-(2-Chlorovinyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (**462**)



Cu(II)Cl (1.15 g, 8.59 mmol, 2.50 equiv) was added to a stirred solution of **461** (1.62 g, 3.43 mmol, 1.00 equiv) in anhydrous THF (0.90 M, 9.5 ml). The resulting suspension was stirred at ambient temperature for 36 h. The reaction mixture was filtered through celite (MeCN) and the filtrate was concentrated *in vacuo*. The crude residue was purified

directly by column chromatography (SiO_2, Et_2O:MeCN 80:20) to afford **462** (609 mg, 82%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 6.41 (d, *J* = 14.6 Hz, 1H, C*H*), 5.98 (d, *J* = 14.6 Hz, 1H, C*H*), 4.24 (d, *J* = 17.2 Hz, 2H, NCH_2), 4.03 (d, *J* = 17.2 Hz, 2H, NCH_2), 2.80 (s, 3H, NCH_3) ppm.

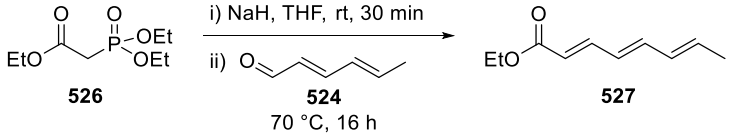
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.3 (C=O), 128.2 (CH), 62.0 (CH_2), 47.4 (CH_3) ppm.

Carbon atom next to boron not observed due to quadrupolar relaxation.

HRMS (ESI) calculated for $C_7H_{10}BClNO_4$ $[M+H]^+$ 218.0391, found 218.0387.

IR (ν_{max}/cm^{-1}, neat). 1749.8, 1608.7, 1567.6, 1452.3, 1298.3 and 1023.4.

Ethyl (2*E*,4*E*,6*E*)-octa-2,4,6-trienoate (**527**)



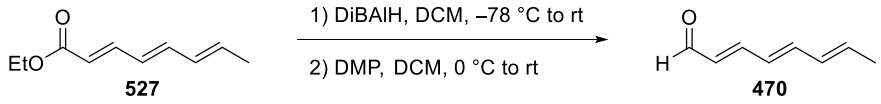
According to a modified literature procedure,[124] ethyl 2-(diethoxyphosphoryl)acetate (**526**) (3.10 ml, 15.6 mmol, 1.50 equiv) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 582 mg, 14.6 mmol, 1.40 equiv) in anhydrous THF (0.28 M, 52 ml) at 0 °C. The resulting mixture was warmed to ambient temperature and stirred for 30 min. Freshly distilled sorbaldehyde (**524**) (1.12 ml, 10.4 mmol, 1.00 equiv) was then added in anhydrous THF (2.68 M, 3.90 ml) and the resulting mixture heated at 70 °C for 16 h. The reaction mixture was diluted with water (50 ml) and Et_2O (50 ml) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 50 ml) and the combined organics were washed with brine (25 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, hexane:EtOAc 95:5) to yield the title compound (**527**) (899 mg, 52%, *E/Z* 8:1) as a pale yellow oil.

All data matched that reported in the literature.[209]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 15.3, 11.3 Hz, 1H, CCHC*H*), 6.52 (dd, *J* = 14.9, 10.7 Hz, 1H, CCHCHCHC*H*), 6.24–6.10 (m, 2H, CCHCHC*H* and CH_3CHC*H*), 5.93 (m, 1H, CH_3C*H*), 5.83 (d, *J* = 15.3 Hz, 1H, CC*H*), 4.20 (q, *J* = 7.1 Hz, 2H, OCH_2), 1.83 (d, *J* = 6.9 Hz, 3H, CHCH_3) 1.29 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (C), 144.9 (CH), 141.1 (CH), 135.2 (CH), 131.4 (CH), 127.7 (CH),120.2 (C) 60.3 (CH_2), 18.7 (CH_3), 14.5 (CH_3) ppm.

(2*E*,4*E*,6*E*)-Octa-2,4,6-trienal (**470**)



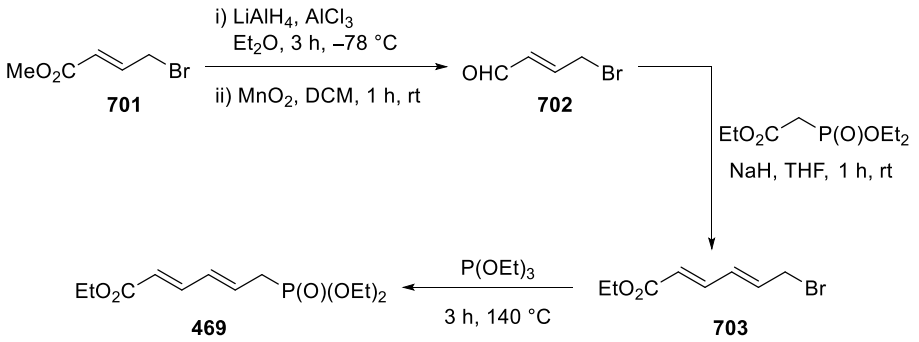
According to a modified literature procedure,[124] DiBAlH (1.00 M in hexane, 11.4 ml, 11.4 mmol, 2.10 equiv) was added dropwise to a stirred solution of polyene **527** (899 mg, 2.40 mmol. 1.00 equiv) in anhydrous DCM (0.40 M, 13.5 ml) at –78 °C. The resulting mixture was warmed to ambient temperature and stirred for 4 h. The reaction was then diluted with Et_2O (20 ml) and quenched through the slow addition of a saturated aqueous solution of Rochelle's salt (100 ml). The reaction was stirred at ambient temperature for 16 h, after which two phases were visible. The phases were separated, and the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was dissolved in anhydrous DCM (0.20 M, 27 ml) and cooled to 0 °C. Dess–Martin periodinane (2.41 g, 5.67 mmol. 1.05 equiv) was added in one portion and the reaction was warmed to ambient temperature and stirred for 18 h. The reaction was filtered through a celite plug (DCM), diluted with a saturated aqueous solution of $NaHCO_3$ (20 ml) and the phases were separated. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, hexane:EtOAc 95:5) to afford the title compound (**470**) (261 mg, 89%, *E/Z* 8:1) as a pale yellow oil.

All data matched that reported in the literature.[209]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J* = 8.0 Hz, 1H, C*H*O), 7.11 (dd, *J* = 14.6, 11.1 Hz, 1H, OCHCHC*H*), 6.64 (dd, *J* = 14.8, 10.6 Hz, 1H, OCHCHCHCHC*H*), 6.38–6.29 (m, 1H, OCHCHCHC*H*), 6.16 (m, 1H, CH_3CHC*H*), 6.13 (m, 1H, OCHC*H*), 6.04 (m, 1H, CH_3C*H*), 1.86 (m, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7 (CH), 152.6 (CH), 143.2 (CH), 137.3 (CH), 131.3 (CH), 130.8 (CH), 127.7 (CH), 18.9 (CH_3) ppm.

Ethyl (2*E*,4*E*)-6-(diethoxyphosphoryl)hexa-2,4-dienoate (**469**)



According to a modified literature procedure,[206] $AlCl_3$ (581 mg, 4.36 mmol, 0.40 equiv) was added portionwise to a stirred suspension of $LiAlH_4$ (451 mg, 12.0 mmol, 1.10 equiv) in anhydrous Et_2O (0.62 M, 19 ml) under an atmosphere of N_2 at –50 °C (acetone/dry ice). The resulting suspension was warmed to ambient temperature and stirred for 30 min, then cooled to –78 °C (acetone/dry ice). A solution of ester **701** (1.31 ml, 10.9 mmol, 1.00 equiv) in anhydrous Et_2O (1.40 M, 7.79 ml) was added dropwise and the resulting mixture was stirred at –78 °C for 3 h. The reaction was warmed to 0 °C (water/ice) and the excess $LiAlH_4$ was quenched according to the Fieser method; specifically, the reaction was sequentially diluted with H_2O (0.5 ml), NaOH (15% aqueous solution, 0.5 ml), H_2O (1.5 ml), and was then warmed to ambient temperature and stirred for 30 min. The mixture was filtered through a pad of celite (Et_2O) and concentrated *in vacuo* to an orange oil. This orange oil was dissolved in DCM (0.31 M, 35 ml) and oven activated MnO_2 (18.95 g, 218 mmol, 20.0 equiv) was added portionwise. The resulting suspension was stirred at ambient temperature for 1 h and was filtered through a celite pad (DCM) and concentrated *in vacuo* to a yellow oil (**702**, 1.43 g), which was used directly in the next step

Triethylphosphonoacetate (2.23 ml, 11.5 mmol, 1.20 equiv) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 460 mg, 11.5 mmol, 1.20 equiv) in anhydrous THF (0.20 M, 48 ml) under a N_2 atmosphere at 0 °C (water/ice). The mixture was stirred until the suspension became clear and then for a further 10 min, at which point it was cooled to –78 °C (acetone/dry ice). **702** (1.43 g, 9.57 mmol, 1.00 equiv) was added and the resulting mixture stirred for 1 h at –78 °C before being warmed to ambient temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl (50 ml) and was diluted with Et_2O (75 ml). The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 50 ml). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column

chromatography (SiO_2, pentane:Et_2O 90:10) to yield vinylogous ester **703** (886 mg, 37% over 3 steps).

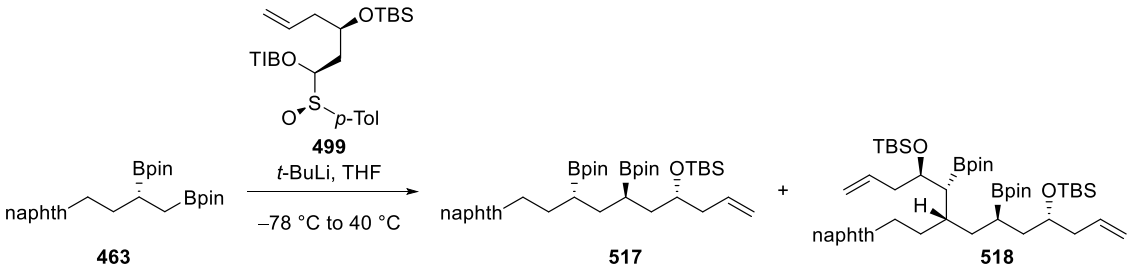
$P(OEt)_3$ (1.04 ml, 6.07 mmol, 1.50 equiv) was added to ester **703** (886 mg, 4.04 mmol, 1.00 equiv) at ambient temperature and heated at 140 °C for 3 h. The reaction was cooled to ambient temperature and the excess $P(OEt)_3$ was removed through azeotropic co-evaporation with toluene (3 x 50 ml) and the crude residue was purified by flash column chromatography (SiO_2, DCM:MeOH 98:2) to yield **469** (276 mg, 83%, *E/Z* 95:5) as a pale yellow oil.

All spectral data matched that reported in the literature.[210,211]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 15.4, 11.1 Hz, 1H, $PCH_2CHCHCH$), 6.30 (ddd, *J* = 15.4, 11.1, 4.8 Hz, 1H, PCH_2CHCH), 6.05 (app sext, 1H, PCH_2CH), 5.85 (dd, *J* = 15.3, 2.3 Hz, 1H, C(O)C*H*), 4.20 (q, *J* = 7.1 Hz, 2H, $C(O)OCH_2$), 4.15–4.05 (m, 4H, 2 x $P(O)OCH_2$), 2.72 (dd, *J* = 23.1, 7.6 Hz, 2H, PCH_2), 1.31 (t, *J* = 7.1 Hz, 6H, 2 x $P(O)OCH_2CH_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $C(O)OCH_2CH_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (C=O), 143.6 (d, *J* = 4.6 Hz, CH), 132.9 (d, *J* = 14.5 Hz, CH), 131.7 (d, *J* = 12.7 Hz, CH), 121.5 (d, *J* = 4.3 Hz, CH), 62.4 (d, *J* = 7.0 Hz, CH_2), 60.5 (CH_2), 32.1 (CH_2), 16.6 (d, *J* = 6.0 Hz, CH_3), 14.43 (CH_3) ppm.

t-Butyldimethyl(((4*S*,6*R*,8*S*)-10-(naphthalen-2-yl)-6,8-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-1-en-4-yl)oxy)silane (**517**)



t-BuLi (1.6 M in pentane, 52 µl, 83 µmol, 1.5 equiv) was added to a stirred solution of 1,2-bis(boronic ester) **463** (24 mg, 55 µmol, 1.0 equiv) and sulfoxide **499** (50 mg, 83 µmol, 1.5 equiv) in anhydrous THF (0.20 M, 0.28 ml) under an atmosphere of N_2 at –78 °C (acetone/dry ice). The resulting mixture was stirred at –78 °C for 1 h. The excess carbenoid was quenched through the dropwise addition of MeOH (HPLC grade, 0.10 ml) and the reaction was warmed to ambient temperature and then heated at 45 °C for 3 h. The reaction was cooled to ambient temperature and the volatile components removed

under high vacuum. The crude residue was purified directly by column chromatography (SiO_2, pentane:Et_2O 96:4) to give 1,3-bis(boronic ester) **517** (10.6 mg, 30%, >95:5 *dr*) as a colourless oil and over homologated product **518** (7.9 mg, 17%, >95:5 *dr*) as a colourless oil.

*Compounds **517** and **518** were part of an unsuccessful model study and were characterised by ^1H NMR only.*

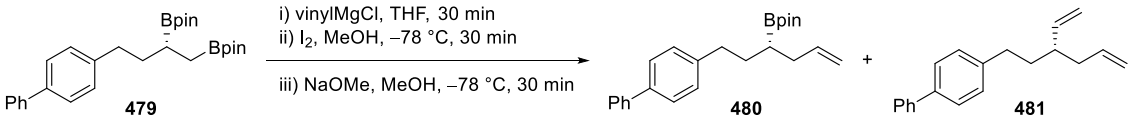
517

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.71 (m, 3H, 3 x Ar*H*), 7.60 (s, 1H, Ar*H*), 7.45–7.31 (m, 3H, 3 x Ar*H*), 5.82 (ddt, *J* = 17.2, 10.4, 7.0 Hz, 1H, C*H*=CH_2), 5.06–4.96 (m, 2H, CH=C*H*$_2$), 3.72 (*app* p, 1H, OC*H*), 2.81–2.73 (m, 2H, ArC*H*$_2$), 2.30–2.21 (m, 1H, CH_2=CHC*H*$_a$H$_b$), 2.21–2.12 (m, 1H, CH_2=CHCH$_a$*H*$_b$), 1.80–1.72 (m, 2H), 1.55–1.36 (m, 6H) 1.27 (s, 24H, 2 x pinacol-C*H*$_3$), 1.15 (*app* d, 9H, SiC(C*H*$_3$)$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$) ppm.

518

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.70 (m, 3H, 3xAr*H*), 7.61 (s, 1H, Ar*H*), 7.45–7.32 (m, 3H, 3xAr*H*), 5.85 (m, 2H, 2 x C*H*=CH_2), 5.09–4.98 (m, 4H, 2x CH=C*H*$_2$), 3.70 (m, 2H, 2xOC*H*), 2.77 (m, 2H, ArC*H*$_2$), 2.29–2.16 (m, 4H, 2 x CH_2=CHC*H*$_2$), 1.80–1.23 (m, 11H), 1.21 (s, 12H, pinacol-C*H*$_3$), 1.16 (s, 12H, pinacol-C*H*$_3$), 0.88 (m, 18H, 2 x SiC(C*H*$_3$)$_3$), 0.08–0.04 (m, 12H, 2 x Si(C*H*$_3$)$_2$) ppm.

(*S*)-2-(1-([1,1'-Biphenyl]-4-yl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**481**)



According to a modified literature procedure,[127] vinyl magnesium chloride (1.6 M in THF, 0.21 ml, 0.33 mmol, 3.0 equiv) was added dropwise to a stirred solution of 1,2-bis(boronic ester) **479** in anhydrous THF (0.22 M, 0.50 ml), at 0 °C (water/ice). The resulting mixture was warmed to ambient temperature and stirred for 30 min. The reaction was then cooled to –78 °C (acetone/dry ice) and a solution of I_2 (84 mg, 0.33 mmol, 3.00 equiv) in anhydrous THF (0.50 M, 0.66 ml) was added dropwise. The reaction was stirred at –78 °C for 30 min. A suspension of NaOMe (17.8 mg, 0.33 mmol, 3.00 equiv)

in anhydrous MeOH (3.0 M, 0.11 ml) was added dropwise and stirred at –78 °C for 30 min. The reaction was warmed to ambient temperature and stirred for 16 h. The excess I_2 was quenched through the addition of a saturated aqueous solution of $Na_2S_2O_3$ (2.0 ml) before the reaction was diluted with Et_2O (5 ml). The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 5 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, pentane:Et_2O 96:4) to yield boronic ester **480** (5.2 mg, 13%) as a colourless oil and diene **481** (18.7 mg, 65%) as a colourless oil.

*Compounds **480** and **481** were part of an unsuccessful model study and were characterised by ^1H NMR only.*

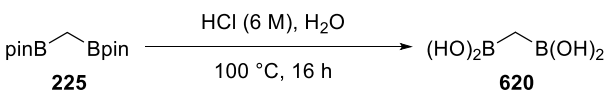
480

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.50 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.43 (m, 2H, Ar*H*), 7.33 (t, *J* = 7.3 Hz, 1H, Ar*H*), 7.27–7.23 (m, 2H, Ar*H*), 5.75 (ddt, *J* = 17.2, 10.2, 8.3 Hz, 1H, C*H*=CH_2), 5.09–4.96 (m, 2H, CH=CH_2), 2.73–2.53 (m, 2H, PhCH_2), 2.37 (m, 1H, BC*H*), 1.80–1.60 (m, 2H, CH_2=CHCH_2), 1.24 (s, 12H, pinacol-CH_3), 1.00–0.87 (m, 2H, ArCH_2CH_2) ppm.

481

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.51 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.43 (m, 2H, Ar*H*), 7.33 (m, 1H, Ar*H*), 7.27–7.23 (m, 2H, Ar*H*), 5.78 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H, C*H*=CH_2), 5.67 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H, C*H*=CH_2), 5.11–4.98 (m, 4H, 2xCH=CH_2), 2.71 (ddd, *J* = 13.7, 10.3, 5.3 Hz, 1H, ArCH_aH_b), 2.58 (ddd, *J* = 13.8, 10.2, 6.2 Hz, 1H, ArCH_aH_b), 1.79 (m, 1H, CH_2=CHCH_aH_b), 1.66–1.56 (m, 1H, CH_2=CHCH_aH_b) 1.35–1.23 (m, ArCH_2CH_2 and C*H*) ppm

<u>Methylenediboronic acid(**620**)</u>



According to a modified literature procedure,[212] HCl (40.4 ml, aqueous, 6.0 M) was added to a stirred suspension of diborylmethane (**225**) (5.00 g, 18.7 mmol, 1.0 equiv) in water (67.5 ml) and the resulting mixture stirred at 100 °C for 16 h. The reaction mixture was cooled to ambient temperature and evaporated to dryness *in vacuo* to afford a green-tinted

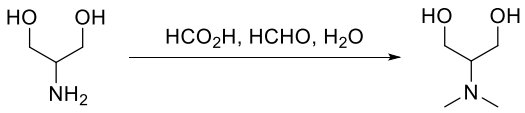
solid. This was triturated in Et_2O and the solid collected by filtration to afford the title compound (**620**) (1.77 g, 92%) as a white solid.

Spectral data in accordance with the published values.[212]

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.00-7.00 (s (br), 4H, (O*H*)$_4$), 0.03 (s, 2H, BC*H*$_2$) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ 5.2 (CH_2) ppm.

2-(Dimethylamino)propane-1,3-diol (**590**)



598 **590**

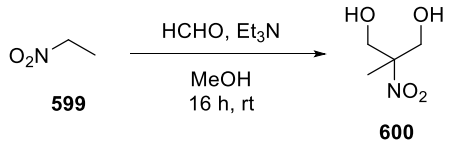
According to a literature procedure,[213] formaldehyde (37% in H_2O, 9.90 ml, 132 mmol, 2.40 equiv) was added to a stirred solution of 2-aminopropane-1,3-diol (**598**) (5.00 g, 54.9 mmol, 1.00 equiv) in formic acid (12.1 ml, 275 mmol, 5.00 equiv) at 0 °C. The reaction mixture was stirred at ambient temperature for 2 h and then at 80 °C for 16 h. The reaction mixture was cooled to ambient temperature and HCl (12.1 M, 0.7 ml) was added and the resulting solution was stirred at ambient temperature for 1 h. The pH value was adjusted to pH 12 by addition of NaOH pellets and the resulting solution was concentrated to dryness *in vacuo*. Excess methanol (100 ml) was added and NaOH removed *via* filtration. The filtrate was concentrated to dryness *in vacuo* and the resulting solid was taken up in chloroform (50 ml), dried over $MgSO_4$, filtered and concentrated to a yellow oil. This oil was purified by Kugelrohr distillation to afford **590** (5.44 g, 83%) as a thick brown oil which solidified under high vacuum to an amorphous brown solid.

Spectral data in accordance with published values.[213]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (d, J = 6.05 Hz, 4H, OC*H*$_2$), 2.62 (p, J = 6.05 Hz, 1H, NC*H*), 2.47 (s (br), 2H, O*H*), 2.39 (s, 6H, NC*H*$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 65.9 (CH_2), 59.9 (CH), 41.6 (CH_3) ppm.

2-Methyl-2-nitropropane-1,3-diol (**600**)



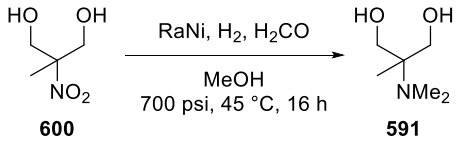
According to a literature procedure,[214] nitroethane (**599**) (4.70 ml, 67.0 mmol, 1.00 equiv) was added dropwise to a stirred solution of formaldehyde (37% in H_2O, 21.0 ml, 280 mmol, 4.20 equiv) and trimethylamine (0.045 ml, 0.32 mmol, 0.05 mol%) in methanol (7.70 ml) at ambient temperature under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was then diluted with EtOAc (100 ml) and water (50 ml), and the phases were separated. The aqueous phase was extracted in EtOAc (3 x 100 ml) and the combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a afford a white solid, which was recrystallised in hot methanol to afford **600** (5.13 g, 57%) as white needles.

Spectral data in accordance with published values.[214]

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.2 (m, 2H, (O*H*)$_2$), 3.77 (dd, J = 11.5, 5.9 Hz, 2H OC*H*$_2$), 3.54 (dd, J = 11.43, 5.57 Hz, 2H, OC*H*$_2$), 1.42 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (101 MHz, CD_3OD) δ 92.28 (C), 64.12 (CH_2), 16.42 (CH_3) ppm.

2-(Dimethylamino)-2-methylpropane-1,3-diol (**591**)



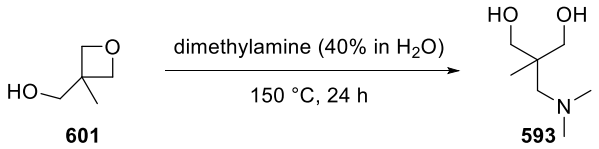
According to a literature procedure,[214] RaNi (0.34 g, 0.68 ml, excess) in MeOH (2.1 ml) was added to an autoclave under a nitrogen atmosphere. A solution of 2-methyl-2-nitropropane-1,3-diol (**600**) (0.50 g, 3.7 mmol, 1.00 equiv) and formaldehyde (0.24 mg, 8.1 mmol, 2.20 equiv) in MeOH (0.77 ml) premixed in a separate Schlenk tube under nitrogen was added to the autoclave reactor. H_2 gas was added to a pressure of 700 psi and the resulting reaction mixture was stirred at 45 °C for 16 h. The pressure was released from the autoclave and the reaction mixture was filtered through a Celite pad (MeOH) under a flow of nitrogen. The filtrate was concentrated *in vacuo* to yield **591** (0.35 g, 70 %) as a colourless oil.

Spectral data in accordance with published values.[214]

^{1}H NMR (400 MHz, $CDCl_3$) δ3.63 (d, *J* = 10.9 Hz, 2H, OC*H*$_2$), 3.57 (d, *J* = 11 Hz, 2H, OC*H*$_2$), 3.07 (s (br), 2H, O*H*), 2.32 (s, 6H, (NC*H*$_3$)$_2$), 0.78 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) 75.2 (C), 71.7 (CH_2), 49.1 (CH_3), 23.7 (CH_3) ppm.

2-((Dimethylamino)methyl)-2-methylpropane-1,3-diol (**593**)



601 **593**

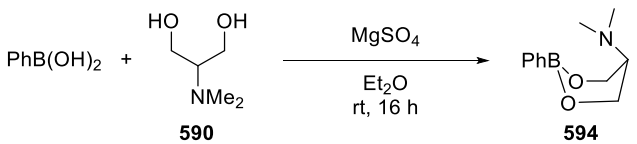
According to a modified literature procedure,[215] dimethylamine (40% in water, 1.50 ml, 12.0 mmol, 2.40 equiv) was added (3-methyloxetan-3-yl)methanol (**601**) (0.49 ml, 4.9 mmol, 1.00 equiv) in a thick walled pressure tube. Without sealing the vessel, the mixture was cooled to −78 °C and left for 5 min. The tube was sealed at −78 °C and was warmed to ambient temperature. The reaction mixture was heated at 150 °C for 24 h. The reaction mixture was cooled to ambient temperature before being concentrated *in vacuo* to afford a colourless oil. The crude residue was purified by bulb to bulb distillation to yield **593** (0.58 g, 80%) as a colourless oil.

Spectral data in accordance with published values.[215]

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.72–3.60 (m, 4H, O(C*H*$_2$)$_2$), 2.49 (s, 2H, NC*H*$_2$), 2.33 (s, 6H, N(C*H*$_3$)$_2$), 0.78 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) *δ* 69.0 (CH_2), 67.6 (CH_2), 48.3 (CH_3), 40.0 (C), 19.5 (CH_3) ppm.

N,*N*-Dimethyl-2-phenyl-1,3,2-dioxaborinan-5-amine (**594**)



590 **594**

2-(Dimethylamino)propane-1,3-diol (**590**) (0.98 mg, 0.82 mmol, 1.00 equiv) was added to a stirred suspension of phenylboronic acid (0.10 mg, 0.82 mmol, 1.00 equiv) and flame-dried $MgSO_4$ (0.99 mg, 0.82 mmol, 1.00 equiv) in Et_2O (2.7 ml) under a nitrogen atmosphere. The resulting reaction mixture was stirred at ambient temperature for 16 h.

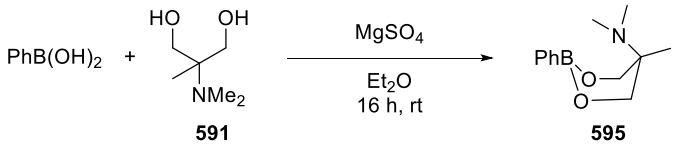
The reaction mixture was filtered through Celite and concentrated *in vacuo* to yield the crude product (**594**) (139 mg, 82%) as a dark orange solid that decomposed on silica gel.

Full characterisation not obtained due to compound instability.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 2H, Ar*H*), 7.40 (m, 1H, Ar*H*), 7.33 (m, 2H, Ar*H*), 4.24 (dd, *J* = 11.0, 3.9 Hz, 2H, NCHCH_2), 4.08 (dd, *J* = 11.0, 7.3 Hz, 2H, NCHCH_2), 2.65 (tt, *J* = 7.5, 3.9 Hz, 1H, NC*H*), 2.37 (s, 6H, N(CH_3)$_2$) ppm.

^{11}B NMR (96 MHz) δ 26.0 ppm.

N,*N*-Trimethyl-2-phenyl-1,3,2-dioxaborinan-5-amine (**595**)



591 **595**

2-(Dimethylamino)-2-methylpropane-1,3-diol (**591**) (100 mg, 0.75 mmol, 1.00 equiv) was added to a stirred suspension of phenylboronic acid (91.5 mg, 0.75 mmol, 1.00 equiv) and flame-dried $MgSO_4$ (90.3 mg, 0.75 mmol, 1.00 equiv) in Et_2O (2.50 ml) under a nitrogen atmosphere. The resulting reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was filtered through Celite and concentrated *in vacuo* to yield **595** as a white solid that decomposed on silica gel.

Full characterisation not obtained due to compound instability.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2H, Ar*H*), 7.39–7.27 (m, 3H, Ar*H*), 3.97–3.90 (m, 4H, (OCH_2)$_2$), 2.33 (s, 6H, (NCH_3)$_2$), 1.05 (s, 3H, CH_3) ppm.

^{11}B NMR (96 MHz) δ 14.9 ppm.

N,*N*-Dimethyl-1-(5-methyl-2-phenyl-1,3,2-dioxaborinan-5-yl)methanamine (**597**)

593 **597**

2-((Dimethylamino)methyl)-2-methylpropane-1,3-diol (**593**) (0.10 mg, 0.69 mmol, 1.00 equiv) was added to a stired suspension of phenylboronic acid (0.83 g, 0.69 mmol, 1.00 equiv) and flame-dried $MgSO_4$ (0.82 mg, 0.69 mmol, 1.00 equiv) in Et_2O (2.30 ml) under a nitrogen atmosphere. The resulting reaction mixture was stirred at ambient temperature

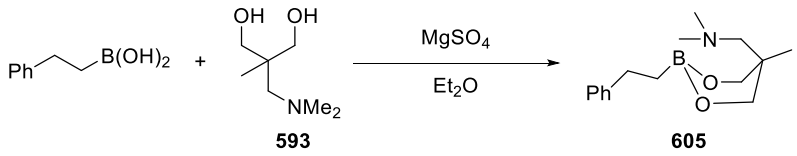
for 16 h. The reaction mixture filtered through Celite and concentrated *in vacuo* to yield the crude product (**597**) as a white solid that was immobile on silica gel.

Full characterisation not obtained due as compound was not purified.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 2H, Ar*H*), 7.25–7.20 (m, 3H, Ar*H*), 3.97 (m, 2H, OCH_2), 3.83 (m, 2H, OCH_2), 2.89 (m, 2H, NCH_2), 2.43 (s, 6H, N(CH_3)$_2$), 0.73 (s, 3H, CH_3) ppm.

^{11}B NMR (96 MHz) δ 3.9 ppm.

N,*N*-Dimethyl-1-(5-methyl-2-phenethyl-1,3,2-dioxaborinan-5-yl)methanamine (**605**)



593 **605**

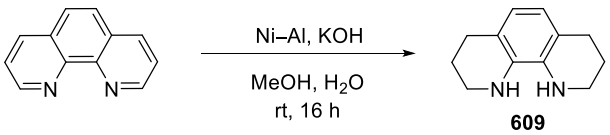
2-((dimethylamino)methyl)-2-methylpropane-1,3-diol (**593**) (0.49 mg, 3.30 mmol, 1.00 equiv) was added to a stirred suspension of phenethylboronic acid (0.50 mg, 3.30 mmol, 1.00 equiv) and flame-dried $MgSO_4$ (0.40 mg, 3.30 mmol, 1.00 equiv) in Et_2O (11 ml) under a nitrogen atmosphere. The resulting reaction mixture was stirred at ambient temperature for 16 h. Reaction mixture filtered through Celite and concentrated *in vacuo* to yield the crude product (**605**) as a white solid that was immobile on silica gel.

Full characterisation not obtained as compound was not purified.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.19 (m, 5H, Ar*H*), 7.10 (m, 1H, Ar*H*), 3.87 (m, 2H, OCH_2), 3.67 (m, 2H, OCH_2), 2.79 (s, 2H, NCH_2), 2.64–2.57 (m, 2H, PhCH_2), 2.53 (s, 6H, N(CH_3)$_2$), 0.68 (s, 3H, CH_3), 0.63–0.57 (m, 2H, BCH_2) ppm.

^{11}B NMR (96 MHz) δ 5.9 ppm.

1,2,3,4,7,8,9,10-Octahydro-1,10-phenanthroline (**609)**



609

According to a modified literature procedure,[168] KOH (2.0 g, 35.0 mmol, 6.36 equiv) in water (6.0 ml) was added to a stirred solution of 1,10-phenanthroline (1.0 g, 5.5 mmol 1.00 equiv) in methanol (11 ml). To this solution was added Ni−Al alloy (4.2 g, excess)

in small portions. Addition of Ni−Al alloy resulted in an exothermic reaction and spontaneous refluxing. The mixture was allowed to reflux without cooling; another portion of Ni−Al was added as it calmed. Following complete addition of Ni−Al, the reaction mixture appeared as a green-tinted black solution and was stirred at ambient temperature for 16 h. The reaction mixture was then diluted with Et_2O (50 ml) and filtered through a Celite plug. The filtrate was concentrated to ~50 ml and water (50 ml) was added. The phases were separated, and the aqueous phase extracted with Et_2O (3 x 50 ml). The combined organics were washed with brine (20 ml), dried over Na_2SO_4, filtered and concentrated to a yellow oil which solidified under high vacuum to afford **609** (897 mg, 86%) as a yellow powder.

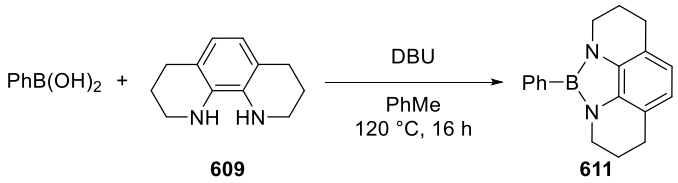
Spectral data in accordance with published values.[168]

***R*f**: 0.25 (pentane/Et_2O, 50:50).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 6.12 (s, 2H, Ar*H*), 4.26 (s, 2H, (N*H*)$_2$), 3.15 (m, 4 H, (NHC*H*$_2$)$_2$), 2.56 (t, *J* = 6.5 Hz, 4H, (NHCH$_2$CH$_2$C*H*$_2$)$_2$), 1.71 (m, 4H, (NHCH$_2$C*H*$_2$)$_2$) ppm.

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 132.4 (C), 118.4 (C), 117.8 (CH), 42.1 (CH_2), 27.4 (CH_2), 22.5 (CH_2) ppm.

5-Phenyl-1,2,3,7,8,9-hexahydro-5*H*-[1,3,2]diazaborolo[1,5,4,3][1,10]phenanthroline **(611)**



To a stirred solution of 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline (**609**) (0.10 mg, 0.53 mmol, 1.00 equiv) and phenylboronic acid (0.71 mg, 0.58 mmol, 1.10 equiv) in toluene (7.92 ml) was added DBU (0.016 ml, 0.11 mmol, 20 mol%). The resulting solution was heated at reflux for 16 h with azeotropic removal of water using a Dean–Stark trap. After this time, the reaction mixture was cooled to ambient temperature and concentrated in *vacuo* to a thick orange oil. This oil was purified by column chromatography (SiO_2, petrol:EtOAc 95:5) to yield **611** (113 mg, 78%) as a purple solid.

***R*f**: 0.51 (petrol/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H, Ar*H*), 7.48–7.39 (m, 3H, Ar*H*), 6.67 (s, 2H, Ar*H*), 3.93–3.89 (m, 4H, $(NCH_2)_2$), 2.90–2.83 (m, 4H, $(NCH_2CH_2CH2)_2$), 2.11–2.03 (m, 4H, $(NCH_2CH_2)_2$) ppm.

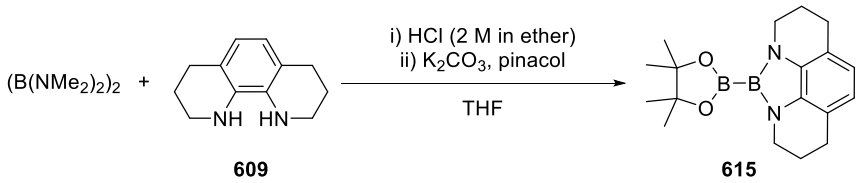
^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0 (CH), 133.0 (C), 128.7 (CH), 128.1 (CH), 118.6 (C), 116.8 (CH), 42.0 (CH_2), 24.8 (CH_2), 23.79 (CH_2) ppm.

^{11}B NMR (128 MHz) δ 26.4 (s).

IR (ν_{max}/cm^{-1}, neat): 2927.25, 1605.06, 1347.37, 987.51 and 698.97.

HRMS: (ESI) calculated for $C_{18}H_{19}BN_2$ $[M+H]^+$ 275.1714, found: 275.1720.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,7,8,9-hexahydro-5*H*-[1,3,2]dizazborolo[1,5,4,3-*lmn*][1,10]phenanthroline (**615**)



According to a modified literature procedure,[158] in a flame-dried Schlenk tube under a nitrogen atmosphere was added freshly distilled tetrakis(dimethylamido)diboron (0.12ml, 0.58 mmol, 1.10 equiv) to anhydrous THF (2.0 M, 0.27 ml), followed by 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline (**609**) (0.10 g, 0.53 mmol, 1.0 equiv), To this solution was added anhydrous HCl (2.0 M in Et_2O, 0.015 ml, 0.03 mmol, 5 mol%) and the resulting solution was stirred at 50 °C for 4 d. At this point, the reaction mixture was basified with K_2CO_3 (0.586 mg, 4.24 mmol, 8.0 equiv). Pinacol (0.076 mg, 0.64 mmol, 1.20 equiv) was then added and the resulting suspension was stirred at 50 °C for 16 h. After this time, the reaction mixture was cooled to ambient temperature and was diluted with water (25 ml) and Et_2O (25 ml). The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 25 ml). The combined ethereal extracts were washed with brine (25 ml), dried over $MgSO_4$, filtered and concentrated in *vacuo* to an orange film. This film was purified by column chromatography (SiO_2, pentane:Et_2O 97:3) to afford **615** (18 mg, 10.5%) as a white solid.

***R*$_f$**: 0.52 (pentane/Et_2O 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 2H, Ar*H*), 4.04–4.01 (m, 4H, NCH_2), 2.84 (t, J = 6.0 Hz, 4H, ($NHCH_2CH_2CH_2$)$_2$), 2.10–2.03 (m, 4H, (NCH_2CH_2)$_2$, 1.32 (s, 6H, BOC(CH_3)$_2$),), 1.31 (s, 6H, BOC(CH_3)$_2$) ppm.

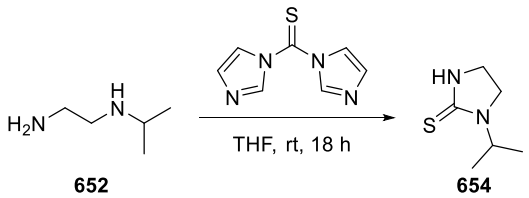
^{13}C NMR (96 MHz, $CDCl_3$) δ 133.6 (C), 118.8 (C), 116.5 (CH), 82.6 (C), 42.6 (CH_2), 25.3 (CH_3), 24.8 (CH_2), 23.9 (CH_2) ppm.

^{11}B NMR (128 MHz) δ 31.9 (s), 23.8 (s) ppm.

IR (ν_{max}/cm^{-1}, neat): 2914.25, 1476.04, 1346.56, 1265.58 and 1041.63.

HRMS: (ESI) calculated for $C_{18}H_{26}B_2N_2O_2$ $[M+H]^+$ 325.2253, found: 325.2260.

1-Isopropylimidazolidine-2-thione (**654**)



652 **654**

According to a modified literature procedure,[177] thiocarbonyldiimidazole (1.704 g, 9.56 mmol, 1.20 equiv) in anhydrous THF (0.80 M, 12.0 mL) was added to a stirred solution of *N*-isopropylethylenediamine (**652**) (0.819 g, 7.97 mmol, 1.00 equiv) in anhydrous THF (0.1 M, 79.7 mL) under a nitrogen atmosphere. The resulting reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated *in vacuo* to a bronze solid which was purified by column chromatography (SiO_2; Et_2O) to a white solid. Recrystallisation from methanol yielded **654** (783.9 mg, 68%) as colourless needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (s(br), 1H, N*H*), 4.79 (hept, J = 6.8 Hz, 1H, NC*H*), 3.62–3.52 (m, 4H, HNCH_2 and $HNCH_2CH_2$), 1.17 (d, J = 6.8 Hz, 6H, NH(CH_3)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.5 (C), 46.9 (CH), 42.9 (CH_2), 41.5 (CH_2), 19.3 (CH_3) ppm.

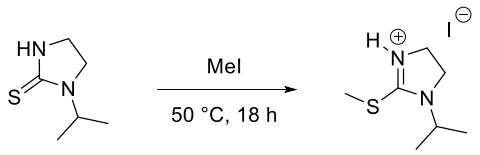
HRMS (ESI) calculated for $C_6H_{13}N_2S$ $[M+H]^+$ 145.0794, found 145.0794.

IR (ν_{max}/cm^{-1}, neat) 3199.1, 1506.7, 1448.1 and 1264.7.

MP 163–164 °C (MeOH).

R_f 0.26 (Et_2O).

4-Isopropyl-5-(methylthio)-3,4-dihydro-2*H*-pyrrol-1-ium iodide (**655**)



654 **655**

According to a modified literature procedure,[177] methyl iodide (3.89 mL, 62.4 mmol, 5.00 equiv) was added dropwise to isopropylimidazolidine-2-thione **22** (1.80 g, 12.5 mmol, 1.00 equiv) at ambient temperature under a nitrogen atmosphere. The resulting mixture was heated at 50 °C (oil bath) for 18 h. The excess methyl iodide was removed *in vacuo* and the residue was taken up in anhydrous MeOH and concentrated (2 x 20 mL) to afford **29** (3.436 g, 96%) as an amorphous yellow solid that was used as such.

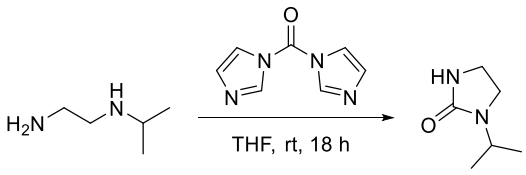
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s (br), 1H, N*H*), 4.10–4.05 (m, 2H, CH_2), 3.97–3.90 (m, 3H, CH_2 and NC*H*), 2.98 (s, 3H, SCH_3), 1.29 (d, *J* = 6.7 Hz, 6H, NC(CH_3)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7 (C), 49.1 (CH), 44.8 (CH_2), 43.5 (CH_2), 19.8 (CH_3), 16.7 (CH_3) ppm.

HRMS (ESI) calculated for $C_7H_{15}N_2S$ $[M+H]^+$ 159.0950, found 159.0956.

IR (ν_{max}/cm^{-1}, neat) 3180.7, 2976.2, 2874.4, 1566.5, 1516.2 and1292.6.

1-Isopropylimidazolidin-2-one (**657**)



652 **657**

According to a modified literature procedure,[177] carbonyldiimidazole (1.904 g, 11.7 mmol, 1.20 equiv) was added portion wise to a stirred solution of *N*-isopropylethylenediamine (**652**) (1.20 mL, 9.78 mmol, 1.00 equiv) in anhydrous THF (0.17 M, 59.0 mL) under a nitrogen atmosphere. The resulting reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was then concentrated under reduced pressure to an orange oil. This oil was diluted with 2 M HCl (200 mL) and dichloromethane (200 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 x 100 mL). The combined organics were dried ($MgSO_4$), filtered

and concentrated *in vacuo* to afford **657** (0.828 g, 66%) as an amorphous white solid that was used as such.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (hept, *J* = 6.6 Hz, 1H, NC*H*), 3.39 (s, 4H, (CH_2)$_2$), 1.12 (d, *J* = 6.6 Hz, 6H, (CH_3)$_2$) ppm.

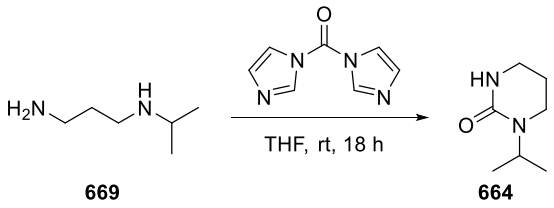
^{13}C NMR (126 MHz, $CDCl_3$) δ 43. 1 (CH), 39.6 (CH_2), 38.5 (CH_2), 19.7 (CH_3) ppm.

HRMS (ESI) calculated for $C_6H_{12}N_2NaO$ $[M+Na]^+$ 151.0842, found 151.0840.

IR (ν_{max}/cm^{-1}, neat) 3198.8, 3086.6, 2974.9, 2866.5 and 1683.1.

R_f 0.17 (96:4 DCM:MeOH).

1-Isopropyltetrahydropyrimidin-2-one (**664**)



669 **664**

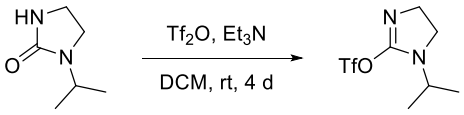
According to a modified literature procedure,[177] carbonyldiimidazole (1.671 g, 10.3 mmol, 1.20 equiv) was added portion wise to a stirred solution of *N*-isopropylpropane-1,3-diamine (**669**) (1.20 mL, 8.61 mmol, 1.00 equiv) in anhydrous THF (0.17 M, 52.2 mL) under a nitrogen atmosphere. The resulting reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was then concentrated *in vacuo* to a colourless oil. This oil was diluted with 2 M HCl (200 mL) and dichloromethane (200 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **664** (0.660 g, 54%) as an amorphous white solid that was used as such.

All data matched that reported in the literature.[216]

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (hept, *J* = 6.6 Hz, 1H, NC*H*), 3.31 (t, *J* = 5.6 Hz, 2H, NCH_2), 3.19 (t, *J* = 5.6 Hz, 2H, NCH_2), 1.91 (*app* p, 2H, NCH_2CH_2), 1.11 (d, *J* = 6.6 Hz, 6H, CH_3)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5 (C), 45.7 (CH), 39.5 (CH_2), 38.2 (CH_2), 21.2 (CH_2), 19.4 (CH_3) ppm.

1-Isopropyl-4,5-dihydro-1*H*-imidazol-2-yl trifluoromethanesulfonate (**659**)



657 **659**

To a stirred solution of 1-isopropylimidazolidin-2-one (**657**) (400 mg, 3.12 mmol, 1.00 equiv) in anhydrous DCM (0.08 M, 39 mL) under a nitrogen atmosphere was added trimethylamine (0.52 mL, 3.74 mmol, 1.20 equiv) followed by the dropwise addition of triflic anhydride (0.63 mL, 3.74 mmol, 1.20 equiv). The resulting mixture was stirred at ambient temperature for 4 d. The reaction mixture was diluted with water (20 mL) and the phases separated. The aqueous phase was extracted with DCM (3 x 50 mL), and the combined organics were, dried over $MgSO_4$ and concentrated *in vacuo* to a crude brown solid. The crude material was purified by column chromatography (SiO_2, DCM) to afford **659** (764.1 mg, 94%) as an amorphous white solid that was used as such.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (hept, *J* = 6.8 Hz, 1H, NC*H*), 4.00–3.96 (m, 2H, NCH_2), 3.49–3.46 (m, 2H, NCH_2), 1.20 (d, *J* = 6.8 Hz, 6H, (CH_3)$_2$) ppm.

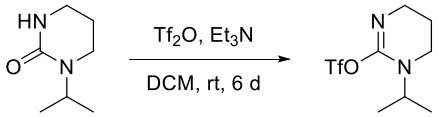
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1 (C), 119.7 (q, $J_{C–F}$ = 323.4 Hz, CF_3), 45.0 (CH), 42.8 (CH_2), 36.8 (CH_2), 19.4 (CH_3) ppm.

HRMS (ESI) calculated for $C_7H_{11}F_3N_2NaO_3S$ $[M+Na]^+$ 283.2204, found 283.0337.

IR (ν_{max}/cm^{-1}, neat) 2989.4, 1742.4, 1396.8 and 1191.1.

R_f 0.54 (Et_2O).

1-Isopropyl-1,4,5,6-tetrahydropyrimidin-2-yl trifluoromethanesulfonate (**670**)



664 **670**

To a stirred solution of 1-isopropyltetrahydropyrimidin-2-one (**664**) (3.204 g, 22.5 mmol, 1.00 equiv) in anhydrous DCM (0.08 M, 281.3 mL) under a nitrogen atmosphere was added trimethylamine (3.80 mL, 27.0 mmol, 1.20 equiv) followed by the dropwise addition of triflic anhydride (4.50 mL, 27.0 mmol, 1.20 equiv). The resulting mixture was stirred at ambient temperature for 6 d. The reaction mixture was diluted with water (200

mL) and the phases separated. The aqueous phase was extracted with DCM (3 x 250 mL), and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to an orange oil. This oil was purified by column chromatography (SiO_2, DCM) to afford **670** (4.984 g, 81%) as an amorphous white solid that was used as such.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (hept, *J* = 6.8 Hz, 1H, NC*H*), 3.86 (*app* t, *J* = 5.8 Hz, 2H, NCH_2), 3.25 (*app* t, *J* = 5.8 Hz, 2H, NCH_2), 2.08 (*app* p, 2H, NCH_2CH_2), 1.17 (d, *J* = 6.8 Hz, 6H, $(CH_3)_2$).

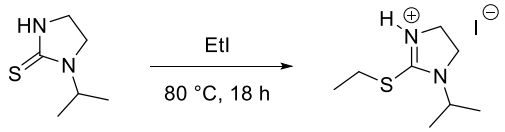
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2 (C), 119.7 (q, $J_{C–F}$ = 323.5 Hz, CF_3), 46.6 (CH), 46.6 (CH_2), 38.8 (CH_2), 22.8 (CH_2), 19.3 (CH_3).

HRMS (ESI) calculated for $C_8H_{13}F_3N_2NaO_3S$ $[M+Na]^+$ 297.0491, found 297.0503.

IR (ν_{max}/cm^{-1}, neat) 1682.9, 1384.6, 1186.4.

R_f 0.54 (Et_2O).

2-(Ethylthio)-1-isopropyl-4,5-dihydro-1*H*-imidazol-3-ium iodide (**689**)



654 **689**

According to a modified literature procedure.[177] Iodoethane (1.39 mL, 17.3 mmol, 5.00 equiv) was added to isopropylimidazolidine-2-thione (**654**) (500 mg, 3.47 mmol, 1.00 equiv) drop wise under a nitrogen atmosphere. The resulting mixture was heated at 80 °C (oil bath) for 18 h. The reaction was cooled to ambient temperature and the excess iodoethane was removed *in vacuo*. The resulting solid was dissolved in anhydrous MeOH and concentrated *in vacuo* (3 x 50 mL) to yield **689** (984 mg, 94%) as an amorphous orange solid which was used as such.

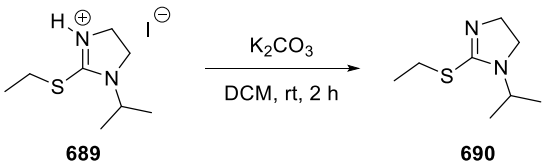
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s (br) 1H, N*H*), 4.09–4.04 (m, 2H, NCH_2), 3.95 (hept, *J* = 6.6 Hz, 1H, NC*H*), 3.94–3.87 (m, 2H, NCH_2), 3.59 (q, *J* = 7.4 Hz, 2H, SCH_2), 1.44 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 1.29 (d, *J* = 6.6 Hz, 6H, $NCH(CH_3)_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8 (C), 48.9 (CH), 44.4 (CH_2), 43.5 (CH_2), 28.5 (CH_2), 19.8 (CH_3), 14.0 (CH_3) ppm.

HRMS (ESI) calculated for $C_8H_{17}N_2S$ $[M]^+$ 173.1107, found 173.1104.

IR (ν_{max}/cm^{-1}, neat) 3141.6, 3021.4, 2967.1, 2947.2, 1557.0 and 1515.7.

2-(Ethylthio)-1-isopropyl-4,5-dihydro-1*H*-imidazole (**690**)



689 **690**

According to a modified literature procedure.[177] To a stirred solution of 2-(ethylthio)-1-isopropyl-4,5-dihydro-1*H*-imidazol-3-ium iodide (**689**) (500 mg, 1.67 mmol, 1.00 equiv) in DCM (0.11 M, 14.9 mL) was added K_2CO_3 (2.308 g, 16.7 mmol, 10.0 equiv). The resulting suspension was stirred at ambient temperature for 2 h. The reaction mixture was filtered through a celite pad eluting with DCM and water (20mL) was added to the mother liquor. The phases were separated, and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo* to yield **690** (241.4 mg, 91%) as a viscous white oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86–3.80 (m, 3H, NC*H* and NCH_2), 3.50 (*app* t, *J* = 9.6 Hz, 2H, NCH_2), 3.24 (q, *J* = 7.4 Hz, 2H, SCH_2), 1.36 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 1.17 (d, *J* = 6.6 Hz, 6H, $NCH(CH_3)_2$) ppm.

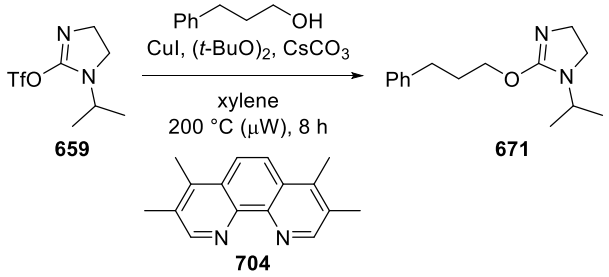
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9 (C), 49.4 (CH_2), 47.1 (CH), 44.1 (CH_2), 26.5 (CH_2), 19.7 (CH_3), 14.4 (CH_3) ppm.

HRMS (ESI) calculated for $C_8H_{17}N_2S$ $[M+H]^+$ 173.1107, found 173.1108.

IR (ν_{max}/cm^{-1}, neat) 2968.7, 2930.0, 2870.5, 1554.3 and 1244.5.

R_f 0.42 (DCM:MeOH 9:1)

1-Isopropyl-2-(3-phenylpropoxy)-4,5-dihydroimidazole (**671**)



According to a modified literature procedure.[217] To a stirred solution of 1-isopropyl-4,5-dihydro-1*H*-imidazol-2-yl trifluoromethanesulfonate (**659**) (2.585 g, 9.90 mmol, 1.00 equiv) in anhydrous xylene (1.0 M, 9.9 mL) in a flame dried microwave vial under a nitrogen atmosphere was added 3-phenyl propan-1-ol (1.35 mL, 9.90 mmol, 1.00 equiv), CuI (95.3 mg, 0.50 mmol, 5.00 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (**704**) (236.3 mg, 1.00 mmol, 10.0 mol%) and $CsCO_3$ (4854.4 mg, 14.9 mmol, 1.50 equiv). The vial was sealed and heated under microwave irradiation at 200 °C for 8 h. Once the reaction had cooled to ambient temperature it was concentrated *in vacuo* to a brown oil. This oil was purified by column chromatography (SiO_2, Et_2O:pentane:DCM 2.5:6.5:1) to yield **671** (886 mg, 36%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H, Ar*H*), 7.23–7.17 (m, 3H, Ar*H*), 4.20 (s(br), 1H, NC*H*), 4.15 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.39 (s(br), 4H, (NCH_2)$_2$), 2.71 (t, *J* = 7.5 Hz, 2H, PhCH_2), 2.01 (*app* p, *J* = 7.5, 6.5 Hz, 2H, OCH$_2$CH_2), 1.15 (d, *J* = 6.8 Hz, 6H, (CH_3)$_2$) ppm.

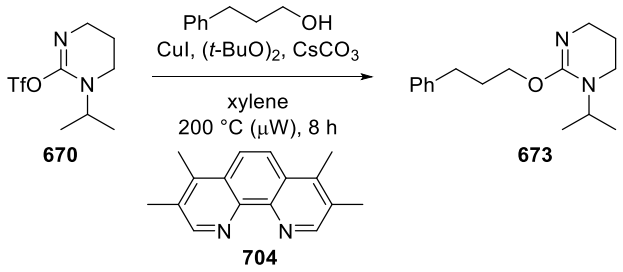
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (C), 128.5 (CH), 128.3 (CH), 126.0 (CH), 65.7 (CH_2), 47.9 (CH), 45.4 (CH_2), 41.9 (CH_2), 32.3 (CH_2), 30.4 (CH_2), 20.7 (CH_3) *quaternary carbon at isourea position not observed.*

HRMS (ESI) calculated for $C_{15}H_{22}N_2NaO$ $[M+Na]^+$ 269.1624, found 269.1633.

IR (ν_{max}/cm^{-1}, neat) 3141.0, 2965.3, 1664.2, 1375.2 and 1188.2.

R_f 0.12 (70:30 pentane:Et_2O).

1-Isopropyl-2-(3-phenylpropoxy)-1,4,5,6-tetrahydropyrimidine (**673**)



According to a modified literature procedure.[217] To a stirred solution of 1-isopropyl-1,4,5,6-tetrahydropyrimidin-2-yl trifluoromethanesulfonate (**670**) (200 mg, 0.73 mmol, 1.00 equiv) in anhydrous xylene (1.0 M, 0.73 mL) in a flame dried microwave vial under an atmosphere of air was added 3-phenyl propan-1-ol (0.10 mL, 0.73 mmol, 1.00 equiv), CuI (7.6 mg, 0.04 mmol, 5.00 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (**704**) (16.5 mg, 0.07 mmol, 10.0 mol%) and $CsCO_3$ (355.1 mg, 1.09 mmol, 1.50 equiv). The vial was sealed and heated under microwave irradiation at 200 °C for 6 h. Once the reaction had cooled to ambient temperature it was concentrated *in vacuo* to a brown oil. This oil was purified by column chromatography (SiO_2, Et_2O:pentane:DCM 2.0:7.5:0.5) to yield the title compound (**673**) (93 mg, 49%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H, Ar*H*), 7.23–7.17 (m, 3H, Ar*H*), 4.14 (t, *J* = 6.5 Hz, 2H, OCH_2), 4.07 (m, 1H, NC*H*), 3.36 (s(br), 2H, NCH_2), 3.27 (t(br), *J* = 5.8 Hz, 2H, NCH_2), 2.70 (t, *J* = 7.6 Hz, 2H, PhCH_2), 1.99 (*app* p(br), *J* = 6.2, 5.6 Hz 2H, OCH_2CH_2), 1.75 (p(br), *J* = 5.8 Hz, 2H, NCH_2CH_2), 1.18 (d, *J* = 6.8 Hz, 6H, (CH_3)$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C), 128.6 (CH), 128.4 (CH), 126.2 (CH), 64.9 (CH_2), 48.2 (CH), 47.9 (CH_2), 46.6 (CH_2) 32.5 (CH_2), 30.9 (CH_2), 30.0 (CH_2), 20.8 (CH_3) ppm.

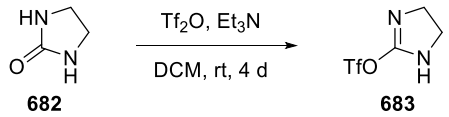
quaternary carbon at isourea position not observed.

HRMS (ESI) calculated for $C_{16}H_{24}N_2NaO$ $[M+Na]^+$ 283.1781, found 283.1790

IR (ν_{max}/cm^{-1}, neat) 3138.3, 2964.8, 1663.1, 1373.5, 1229.2 and 1186.1.

R_f 0.12 (70:30 pentane:Et_2O).

4,5-Dihydroimidazol-2-yl trifluoromethanesulfonate (**683**)



To a stirred solution of imidazolidin-2-one (**682**) (1.00 g, 11.6 mmol, 1.00 equiv) in anhydrous DCM (0.3 M, 38.7 mL) under a nitrogen atmosphere at 0 °C was added trimethylamine (1.94 mL, 13.9 mmol, 1.20 equiv) followed by the dropwise addition of triflic anhydride (2.34 mL, 13.9 mmol, 1.20 equiv). The resulting mixture was stirred at ambient temperature for 4 d. The reaction mixture was then diluted with water (100 mL) and the phases separated. The aqueous phase was extracted with DCM (3 x 50 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to an orange oil. This oil was purified by column chromatography (SiO_2; DCM:MeOH 98:2) to afford **683** (883.6 mg, 35%) as an amorphous white solid that was used as such.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (s(br), 1H, N*H*), 4.10 (*app* t, *J* = 7.8 Hz, 2H, NCH_2), 3.62 (*app* t, 2H, NCH_2) ppm.

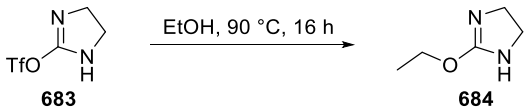
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (C), 100.0 (C), 45.4 (CH_2), 37.4 (CH_2) ppm.

HRMS (ESI) calculated for $C_4H_5F_3N_2NaO_3S$ $[M+Na]^+$ 240.9865, found 240.9876.

IR (ν_{max}/cm^{-1}, neat) 3256.8, 3171.2, 1754.1, 1399.2, 1192.3.

R_f 0.20 (Et_2O).

2-Ethoxy-4,5-dihydro-1*H*-imidazole (**684**)



4,5-dihydroimidazol-2-yl trifluoromethanesulfonate (**683**) (250 mg, 1.15 mmol, 1.00 equiv) was heated at 90 °C (oil bath) in anhydrous EtOH (5 mL) for 16 h. The reaction was cooled to ambient temperature and concentrated *in vacuo* to a light brown oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 1:1) to yield the title compound (**684**) (118.7 mg, 90%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (s(br), 1H, N*H*), 4.13 (q, *J* = 7.0 Hz, 2H, OCH_2), 3.45–3.35 (m, 4H, 2xNCH_2), 1.26 (t, *J* = 7.0 Hz, 3H, CH_3) ppm.

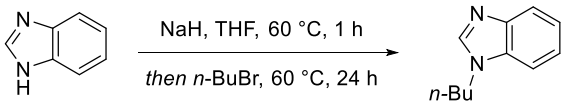
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (C), 61.8 (CH_2), 45.3 (CH_2), 40.8 (CH_2), 14.5 (CH_3) ppm.

HRMS (ESI) calculated for $C_8H_{16}N_2NaO$ $[M+Na]^+$ 179.1155, found 179.1148.

IR (ν_{max}/cm^{-1}, neat) 3433.7, 3136.5, 1689.0, 1528.3, 1367.7 and 1268.3.

R_f 0.19 (1:1 pentane:Et_2O).

1-Butyl-1*H*-benzimidazole (**692**)



691 **692**

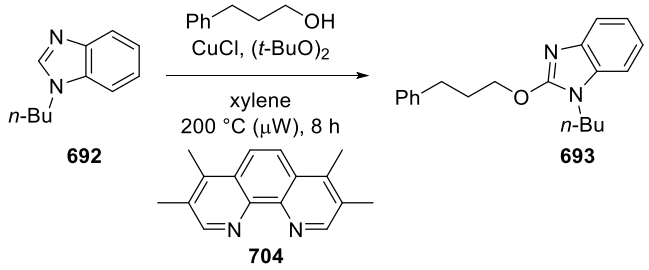
According to a modified literature procedure.[218] To a suspension of NaH (60% dispersion in mineral oil, 2.032 g, 50.8 mmol, 1.20 equiv) in anhydrous THF (0.68 M, 74.7 mL) was added benzimidazole (**691**) (5.00 g, 42.3 mmol, 1.00 equiv) portion wise. The resulting suspension was heated for 1 h at 60 °C (oil bath). A solution of *n*-butylbromide (4.99 mL, 46.6 mmol, 1.10 equiv) in anhydrous THF (0.93 M, 50.0 mL) was added over 10 min. The resulting reaction mixture was heated at 60 °C (oil bath) for 24 h. After this time the reaction mixture was concentrated *in vacuo*. The resulting residue was diluted with DCM (200 mL) and water (200 mL). The phases were separated, and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organics were, dried ($MgSO_4$), filtered and concentrated *in vacuo* to an orange oil. This oil was purified by column chromatography (SiO_2; 5% MeOH in DCM) to afford an orange oil which was identified as a mixture of the title compound and mineral oil. This oil was diluted with petroleum ether (50 mL) and acetonitrile (50 mL). The phases were separated, and the petroleum ether layer was extracted with acetonitrile (3 x 10 mL). The combined acetonitrile layers were concentrated *in vacuo* to afford **692** (6.524 g, 89%) as a yellow oil.

All data matched that reported in the literature.[218]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, NC*H*), 7.81 (m, 1H, Ar*H*), 7.39 (m, 1H, Ar*H*), 7.32 – 7.25 (m, 2H, Ar*H*), 4.16 (t, *J* = 7.2 Hz, 2H, NCH_2), 1.85 (*app* p, *J* = 7.5, 7.2 Hz, 2H, NCH_2CH_2), 1.35 (*app* sext, *J* = 7.5, 7.4 Hz, 2H, $NCH_2CH_2CH_2$), 0.95 (t, *J* = 7.4 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 142.9 (CH), 133.8 (C), 122.7 (CH), 121.9 (CH), 120.4 (CH), 109.6 (CH), 44.8 (CH_2), 31.8 (CH_2), 20.0 (CH_2), 13.5 (CH_3) ppm.

1-Butyl-2-(3-phenylpropoxy)-1*H*-benzimidazole (**693**)



According to a modified literature procedure.[217] To a solution of 1-butyl-1*H*-benzimidazole (**692**) (1.00 g, 5.74 mmol, 1.00 equiv) in anhydrous xylene (0.5 M, 11.5 mL) in a flame dried microwave vial under a nitrogen atmosphere was added 3-phenyl propan-1-ol (0.78 mL, 5.74 mmol, 1.00 equiv), CuCl (28.4 mg, 0.29 mmol, 5.00 mol%), di *t*-butylperoxide (2.12 mL, 11.5 mmol, 2.00 equiv) and 3,4,7,8-tetramethyl-1,10-phenanthroline (**704**) (67.8 mg, 0.29 mmol, 5.00 mol%). The vial was sealed and heated under microwave irradiation at 200 °C for 6 h. Once the reaction had cooled to ambient temperature it was concentrated *in vacuo* to a brown oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 70:30) to yield **693** (363.8 mg, 21%) as an amber oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 1H, Ar*H*), 7.33–7.27 (m, 2H, Ar*H*), 7.24–7.20 (m, 3H, Ar*H*), 7.19–7.13 (m, 3H, Ar*H*), 4.58 (t, *J* = 6.4 Hz, 2H, OCH_2), 3.96 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.82 (*app* t, 2H, $OCH_2CH_2CH_2$), 2.24–2.16 (m, 2H, OCH_2CH_2), 1.76 (*app* p, *J* = 7.0, 7.6 Hz, 2H, NCH_2CH_2), 1.36 (*app* sext, *J* = 7.4, 7.6 Hz, 2H, $NCH_2CH_2CH_2$), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3) ppm.

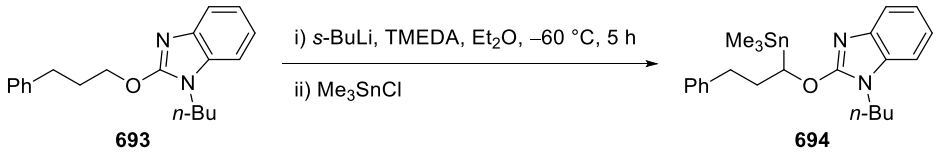
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (C), 140.1 (C), 133.7 (C), 128.5 (CH), 128.4 (CH), 126.0 (CH), 121.2 (CH), 120.7 (CH), 117.6 (CH), 108.1 (CH), 69.4 (CH_2), 41.7 (CH_2), 32.1 (CH_2), 31.1 (CH_2), 30.6 (CH_2), 20.0 (CH_2), 13.7 (CH_3) ppm. *quaternary carbon at isourea position not observed.*

HRMS (ESI) calculated for $C_{20}H_{24}N_2NaO$ $[M+Na]^+$ 331.1781, found 331.1771.

IR (ν_{max}/cm^{-1}, neat) 2954.3, 1708.2, 1621.0, 1535.5 and 1455.2.

R_f 0.21 (70:30 pentane:Et_2O).

1-Butyl-2-(3-phenyl-1-(trimethylstannyl)propoxy)-1*H*-benzimidazole (**694**)



693 **694**

According to a modified literature procedure.[52] To a stirred solution of 1-butyl-2-(3-phenylpropoxy)-1*H*-benzimidazole (**693**) (50.0 mg, 0.16 mmol, 1.00 equiv) in THF (0.33 M, 0.48 mL) was added TMEDA (0.03 mL, 0.21 mmol, 1.30 equiv). The resulting solution was cooled to –60 °C (acetone/dry ice) and *s*-BuLi (0.16 mL, 0.21 mmol, 1.30 equiv) was added dropwise over 2 min. The reaction was stirred at –60 °C (acetone/dry ice) for 5 h, after which Me_3SnCl (1.00 M in hexanes, 0.21 mL, 0.21 mmol, 1.30 equiv) was added dropwise over 2 min. The reaction was warmed to ambient temperature and stirred at this temperature for 16 h. The volatiles were removed under high vacuum and the residue purified by column chromatography (SiO_2, pentane:Et_2O 90:10) to afford **694** (46 mg, 61%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H, Ar*H*), 7.25–7.22 (m, 2H, Ar*H*), 7.19–7.11 (m, 6H, Ar*H*), 5.31 (dd, *J* = 10.2, 3.8 Hz, 1H, OC*H*), 3.95 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.79 (ddd, *J* = 13.6, 10.8, 5.6 Hz, 1H, OCHCH$_2$C*H*^{a}H^b), 2.72 (m, 1H, OCHCH$_2$CH^a*H*^{b}), 2.15 (m, 1H, OCHC*H*^{a}H^b), 2.06 (dddd, *J* = 14.3, 10.8, 6.2, 3.8 Hz, 1H, OCHCH^a*H*^{b}), 1.83–1.71 (m, 2H, NCH$_2$CH_2), 1.40 (p, *J* = 7.5 Hz, 2H, CH$_3$CH_2), 0.96 (t, *J* = 7.5 Hz, 3H, CH_3), 0.10 (s, 9H, Sn(CH_3)$_3$) ppm.

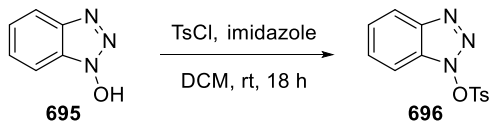
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C), 142.0 (C), 140.1 (C), 133.9 (C), 128.3 (CH), 128.3 (CH), 125.8 (CH), 121.0 (CH), 120.3 (CH), 117.4 (CH), 107.9 (CH), 75.7 (CH), 41.6 (CH_2), 33.7 (CH_2), 33.6 (CH_2), 31.2 (CH_2), 20.1 (CH_2), 13.7 (CH_3), –3.5 (CH_3) ppm.

HRMS (ESI) calculated for $C_{23}H_{33}N_2OSn$ $[M+H]^+$ 473.1613, found 473.1613.

IR (ν_{max}/cm^{-1}, neat) 2957.8, 2928.8, 2861.4, 1621.0, 1534.1 and 1455.4.

R_f 0.76 (7:3 pentane:Et_2O).

1*H*-Benzo[1,2,3]triazol-1-yl 4-methylbenzenesulfonate (**696**)



695 **696**

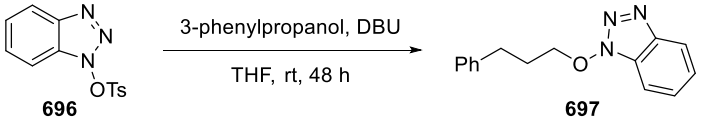
To a stirred solution of HOBt hydrate (**695**) (500 mg, 3.70 mmol, 1.00 equiv) in anhydrous DCM (0.25 M, 14.8 mL) under nitrogen atmosphere was added imidazole (256.7 mg, 3.77 mmol, 1.02 equiv). The resulting solution was cooled to 0 °C (ice/ water) and a solution of freshly recrytallised tosyl chloride (712.8mg, 3.74 mmol 1.01 equiv) in anhydrous DCM (1.90 M, 1.97 mL) was added dropwise over 2 min. The reaction mixture was warmed to ambient temperature and stirred for 18 h. The reaction was then diluted with DCM (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. This oil was purified by column chromatography (SiO_2, pentane:Et_2O 80:20) to yield **696** (792.2 mg, 74%) as an amorphous white solid that was used as such.

All data matched that reported in the literature.[219]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (m, 1H, Ar*H*), 7.80–7.75 (m, 2H, Ar*H*), 7.65 (m, 1H, Ar*H*), 7.59 (m, 1H, Ar*H*), 7.46–7.38 (m, 3H, Ar*H*), 2.50 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (C), 142.9 (C), 130.5 (CH), 129.8 (CH), 129.3 (CH), 129.0 (C), 128.7 (C), 125.3 (CH), 120.3 (CH), 109.5 (CH), 22.0 (CH_3) ppm.

1-(3-Phenylpropoxy)-1*H*-benzo[1,2,3]triazole (**697**)



696 **697**

To a stirred solution of 1*H*-benzo[1,2,3]triazol-1-yl 4-methylbenzenesulfonate **696** (20 mg, 0.69 mmol, 1.00 equiv) in anhydrous THF (0.2 M, 3.45 mL) under a nitrogen atmosphere was added 3-phenyl propan-1-ol (0.11 mL, 0.82 mmol, 1.20 equiv) followed by the dropwise addition of DBU (0.12 mL, 0.83 mmol, 1.20 equiv). The reaction was stirred at ambient temperature for 48 h. The volatiles were removed under high vacuum and the residue was purified by column chromatography (SiO_2, pentane:Et_2O 90:10) to yield **697** (121.7 mg, 70%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 1H, Ar*H*), 7.58–7.48 (m, 2H, Ar*H*), 7.39 (m, 1H, Ar*H*), 7.35–7.29 (m, 2H, Ar*H*), 7.25–7.20 (m, 3H, Ar*H*), 4.57 (t, *J* = 6.5 Hz, 2H, OC*H*$_2$), 2.92 (t, *J* = 7.2 Hz, 2H, PhC*H*$_2$), 2.25–2.16 (m, 2H, OCH$_2$C*H*$_2$) ppm.

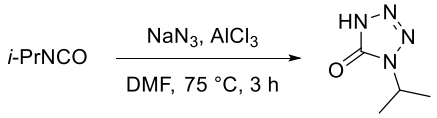
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 140.5 (C), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.3 (C), 126.3 (CH), 124.6 (CH), 120.3 (CH), 108.6 (CH), 79.8 (CH_2), 31.7 (CH_2), 29.6 (CH_2) ppm.

HRMS (ESI) calculated for $C_{15}H_{16}N_3O$ $[M+H]^+$ 254.1288, found 254.1294.

IR (ν_{max}/cm^{-1}, neat) 3025.7, 1496.3, 1366.6, 1239.3.

R_f 0.33 (7:3 pentane:Et_2O)

1-Isopropyl-1,4-dihydro-5*H*-tetrazol-5-one (**698**)



698

Anhydrous $AlCl_3$ (740.5 mg, 5.56 mmol, 1.10 equiv) was added to anhydrous DMF (0.5 M, 10.1 mL) at 0 °C (ice/ water) and was stirred for 15 min. NaN_3 (328 mg, 5.05 mmol, 1.00 equiv) was added and the resulting mixture stirred for a further 15 min. Isopropyl isocyanate (0.57 mL, 5.05 mmol, 1.00 equiv) was then added and the resulting solution stirred at 75 °C (oil bath) for 3 h. The reaction mixture was cooled to ambient temperature and poured onto a stirring mixture of $NaNO_2$ (500 mg), water (100 mL) and ice (2.00 g). The resulting mixture was acidified with HCl (10% aq, 100 mL) and diluted with EtOAc (100 mL) The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (SiO_2, pentane:Et_2O 88:12) to afford **698** (372.2 mg, 49 %) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) 4.96 (s(br), 1H, N*H*), 3.91 (hept, *J* = 6.7 Hz, 1H, C*H*), 1.17 (d, *J* = 6.7 Hz, 6H, 2 x C*H*$_3$).

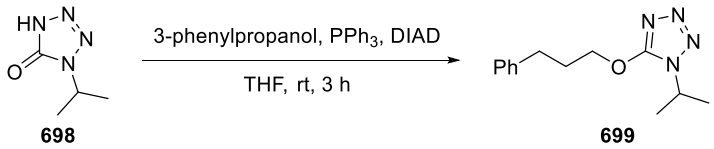
^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C), 43.4 (CH), 22.6 (CH_3).

HRMS (ESI) calculated for $C_4H_8N_4NaO$ $[M+Na]^+$ 151.0590, found 151.0598.

IR (ν_{max}/cm^{-1}, neat) 3322.9, 2977.5, 2143.4, 1617.5, 1535.4, 1474.5 and 1339.6.

R_f 0.45 (70:30 pentane:Et_2O).

1-Isopropyl-5-(3-phenylpropoxy)-1*H*-tetrazole (**699**)



698 **699**

According to a modified literature procedure.[185] To a stirred solution of PPh_3 (390.8 mg, 1.49 mmol, 1.10 equiv), 3-phenyl propan-1-ol (0.19 mL, 1.36 mmol, 1.00 equiv) and 1-isopropyl-1,4-dihydro-5*H*-tetrazol-5-one (**698**) (200 mg, 1.56 mmol, 1.15 equiv) in anhydrous THF (0.66 M, 10.1 mL) under a nitrogen atmosphere was added DIAD (0.29 mL, 1.49 mmol, 1.10 equiv) dropwise. The resulting reaction mixture was stirred at ambient temperature for 3 h before the volatiles were removed *in vacuo*. The crude residue was purified by column chromatography (Si_2O, pentane:Et_2O 4:1) to yield **699** (106.4 mg, 32%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) 7.33–7.28 (m, 2H, Ar*H*), 7.23–7.19 (m, 3H, Ar*H*), 4.10 (t(br), *J* = 6.5 Hz, 2H, OCH_2), 3.90–3.78 (m(br), 1H, C*H*), 2.71 (t, *J* = 7.8 Hz, 2H, PhCH_2), 2.00–1.92 (m(br), 2H, OCH_2CH_2), 1.18 (d, 6.5 Hz, 6H, 2xCH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8 (C), 141.5 (C), 128.4 (CH) 128.4 (CH), 125.9 (CH), 64.0 (CH_2), 43.0 (CH), 32.2 (CH_2), 30.7 (CH_2), 23.1 (CH_3) ppm.

HRMS (ESI) calculated for $C_{13}H_{18}N_4NaO$ $[M+Na]^+$ 269.1373, found 269.1366.

IR (ν_{max}/cm^{-1}, neat) 3324.1, 2972.6, 1681.5, 1527.9, 1454.7, 1256.1 and 1097.8.

R_f 0.52 (1.5:1 pentane:Et_2O).

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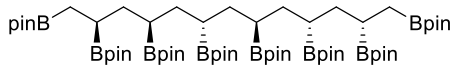
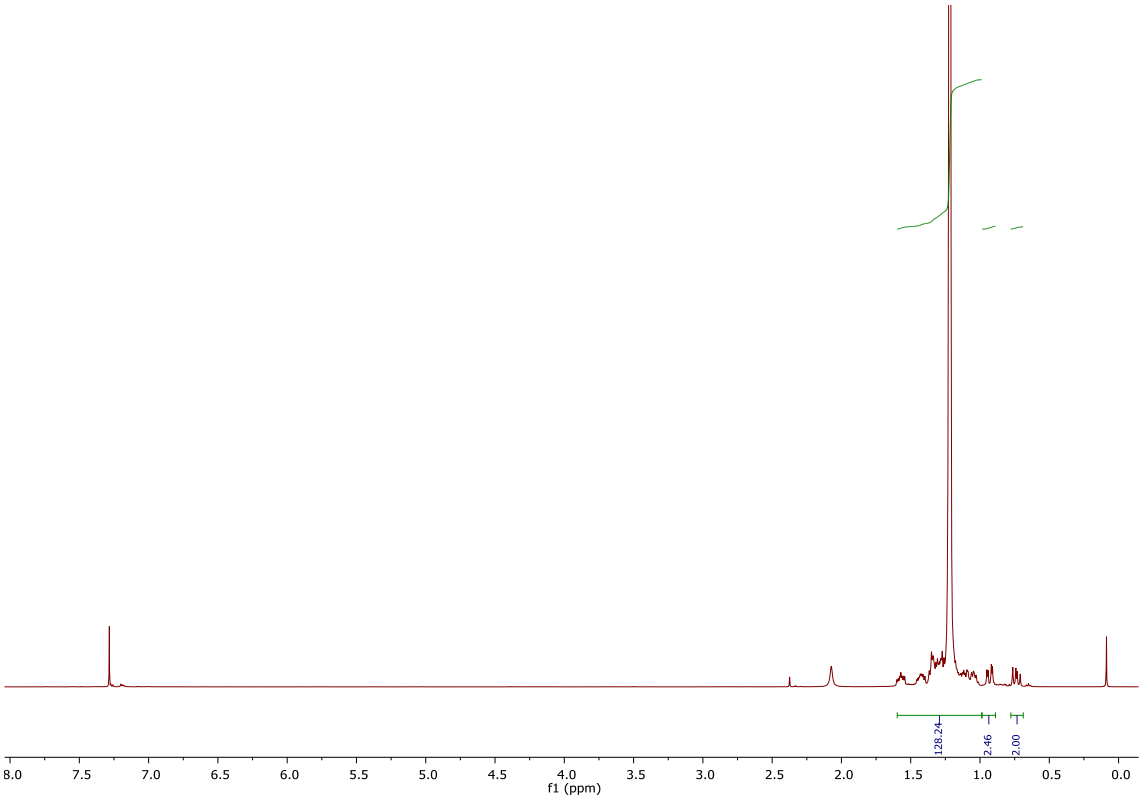
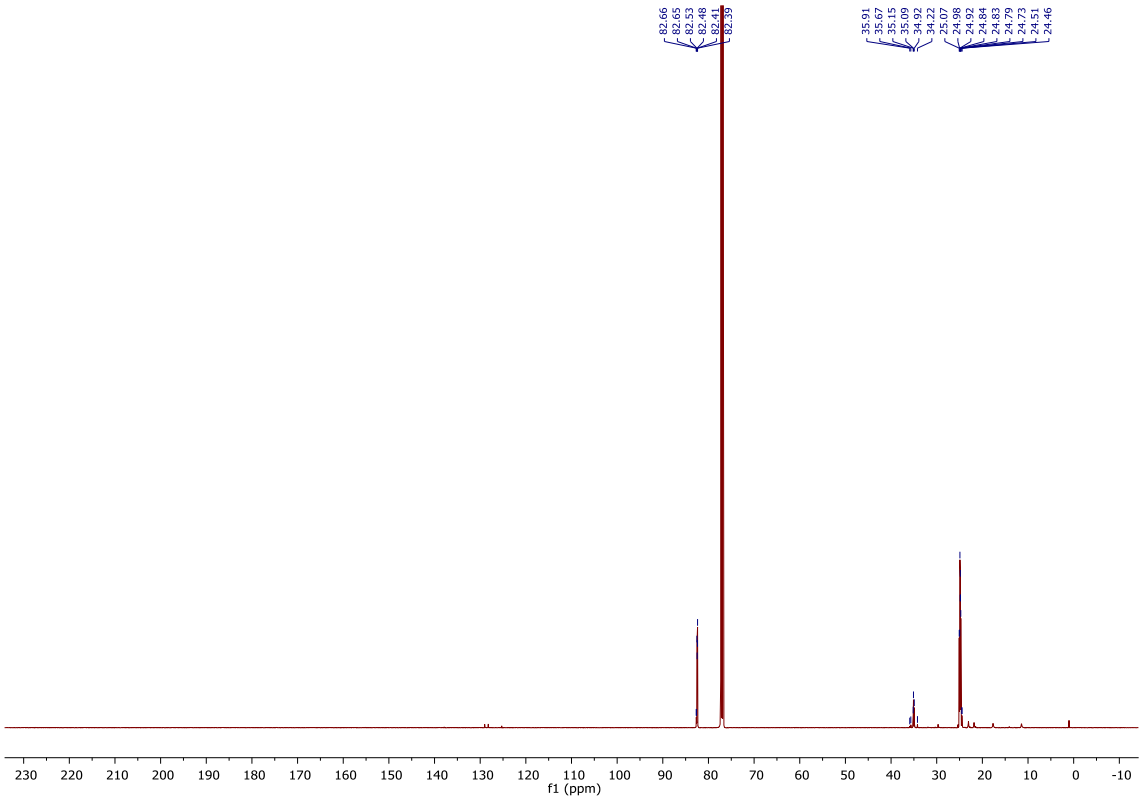
Appendix

Selected NMR spectra

*Compound **444***






82.66
82.65
82.53
82.48
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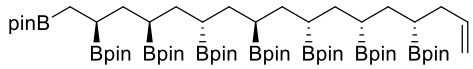
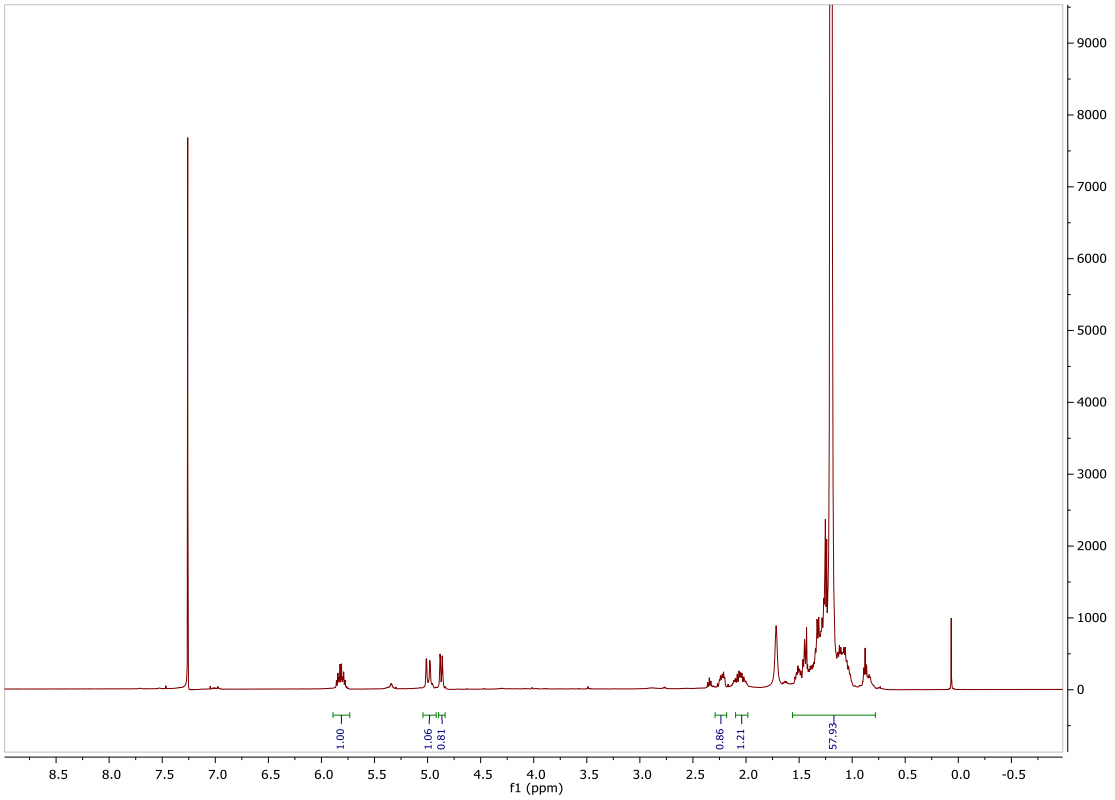
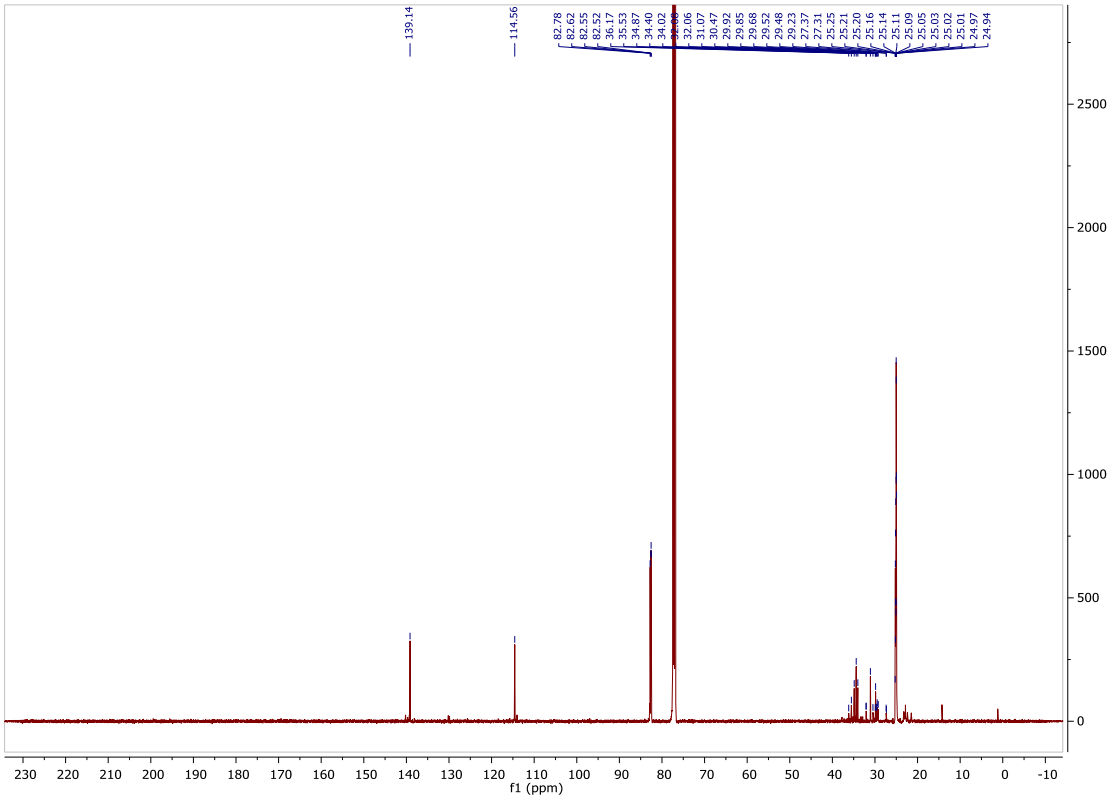
82.39
35.91
35.67
35.15
35.09
34.92
34.22
25.07
24.98
24.92
24.84
24.83
24.79
24.73
24.51
24.46
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

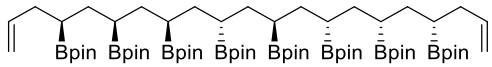
*Compound **450***

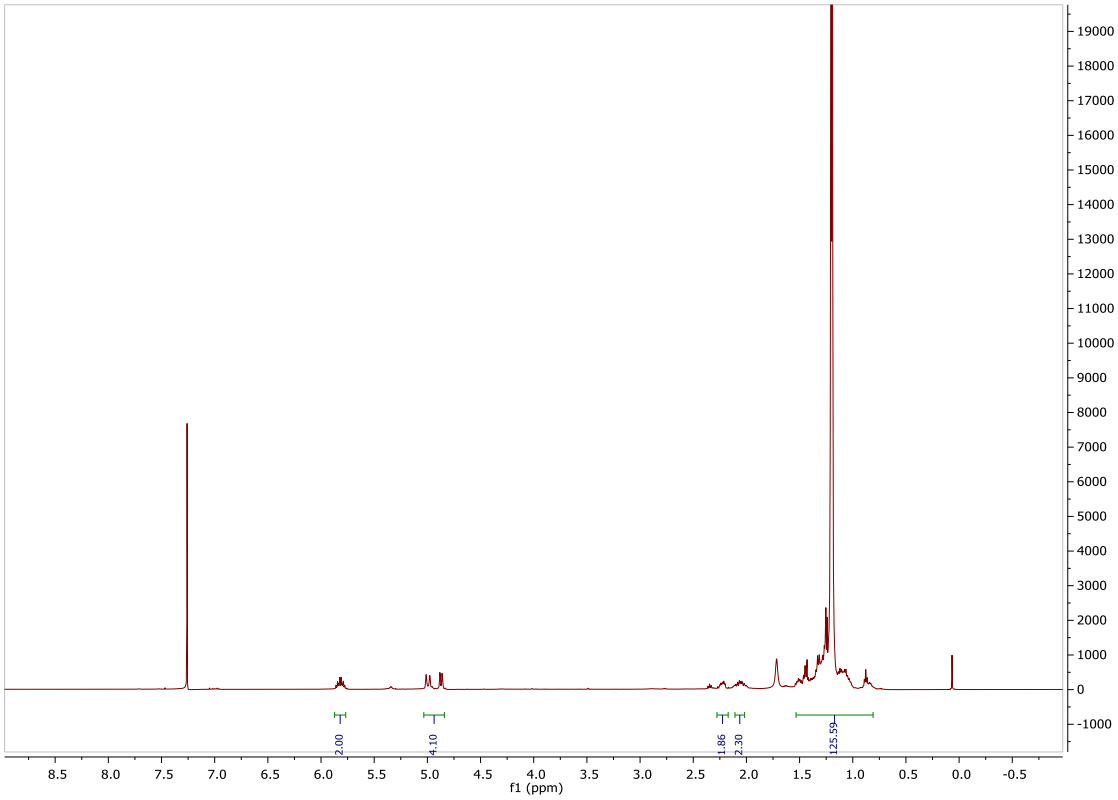


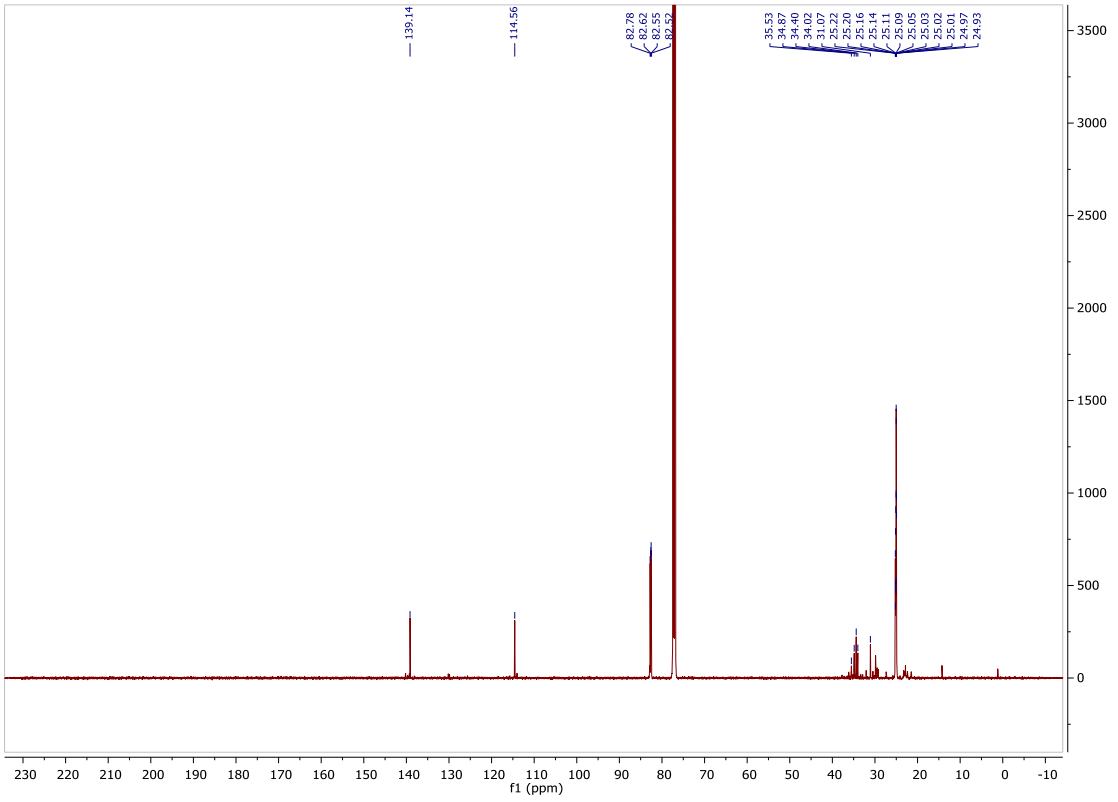




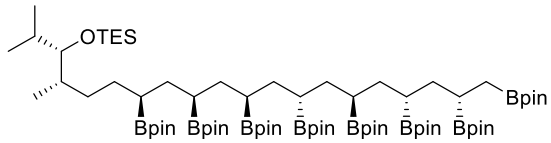
*Compound **451***

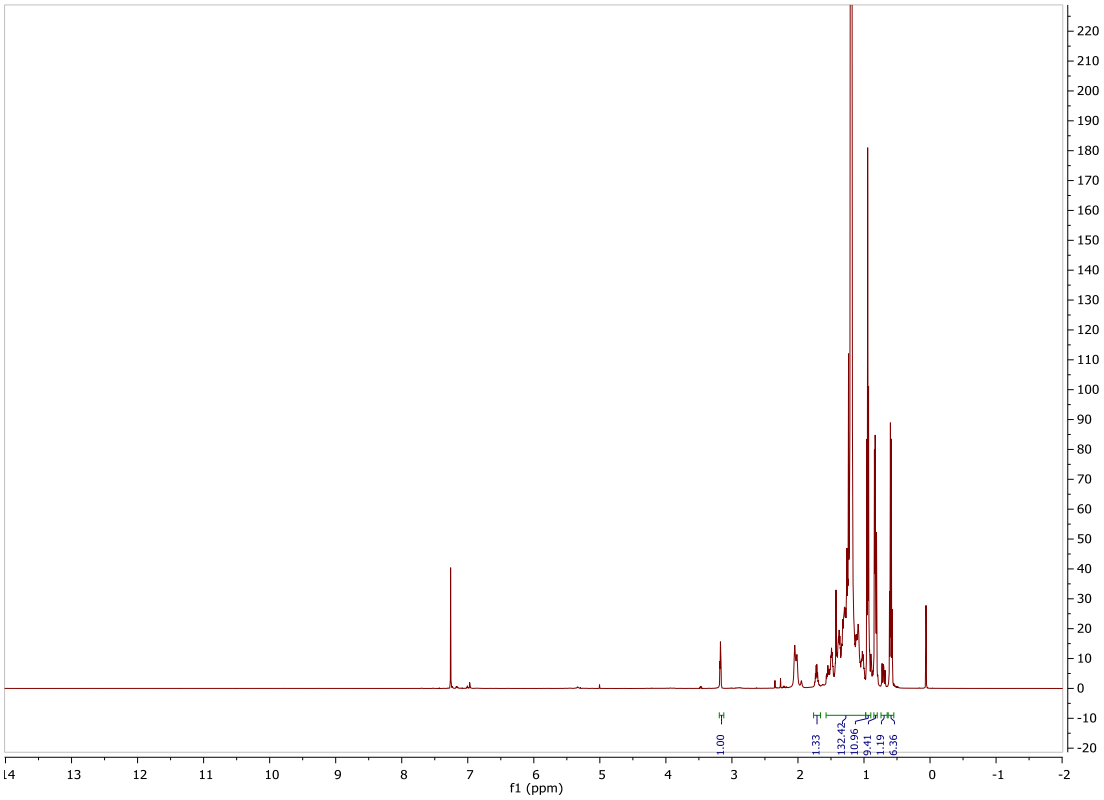


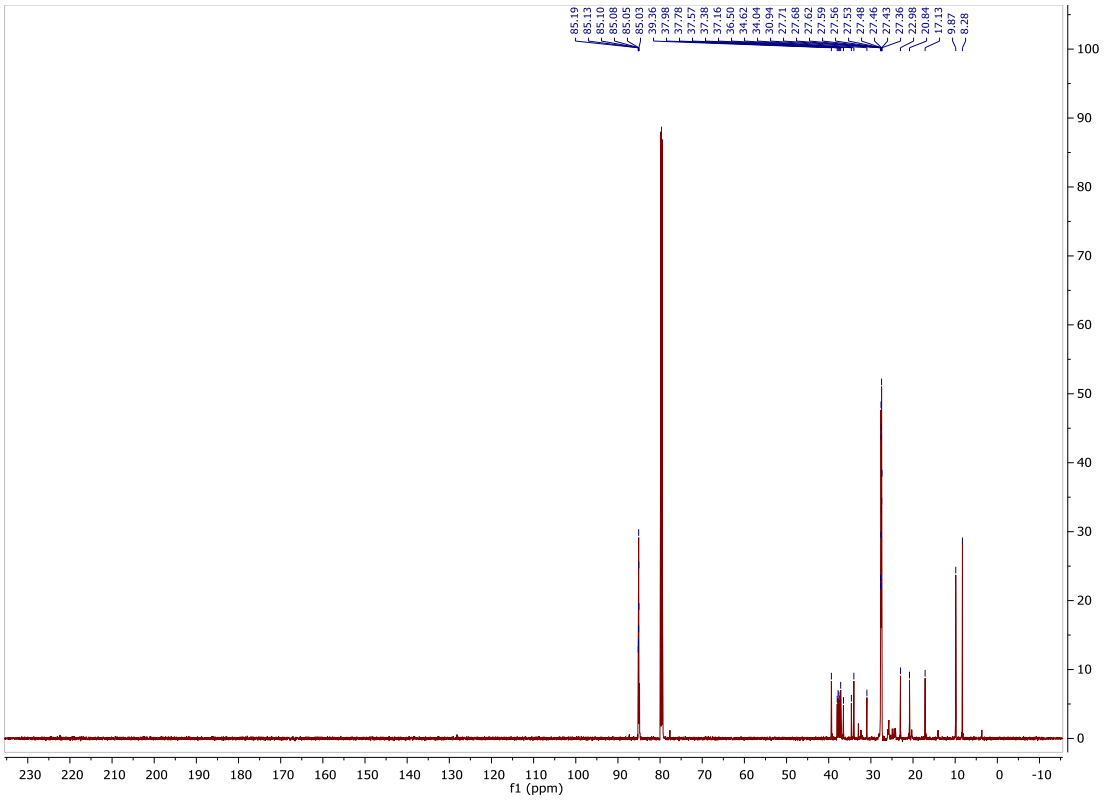




*Compound **498***







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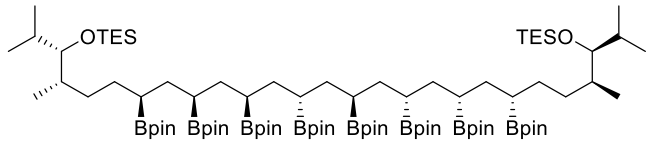

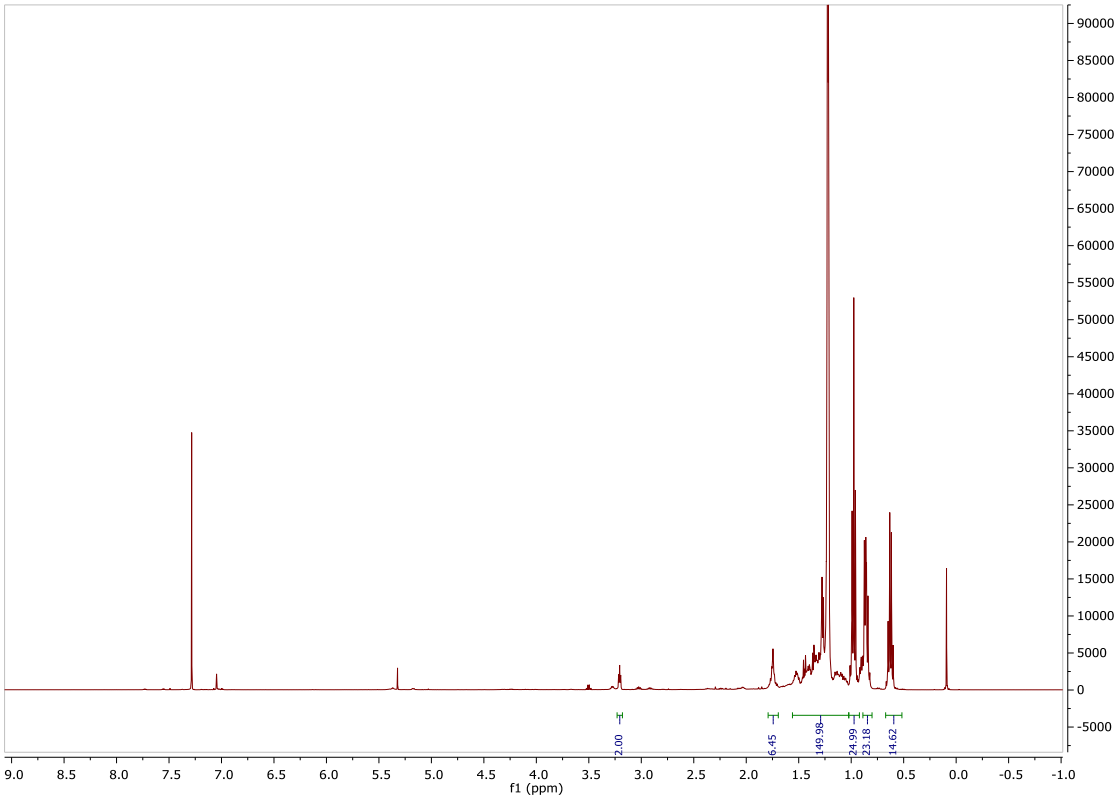

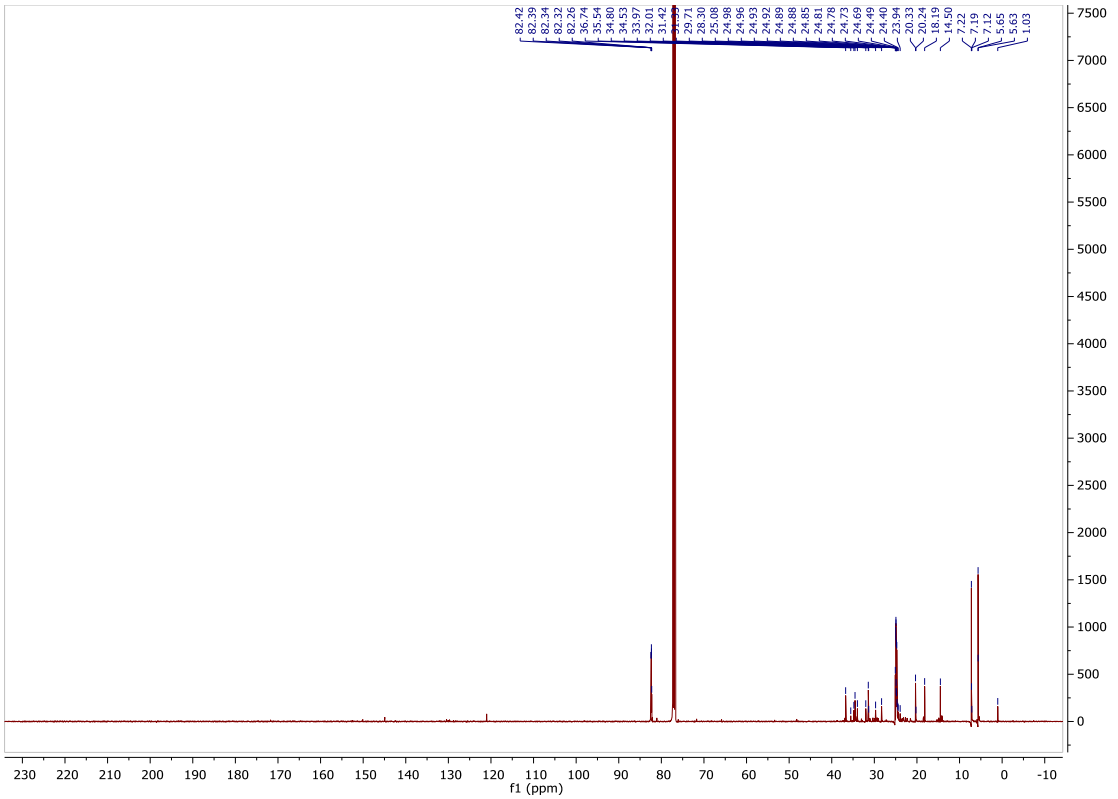

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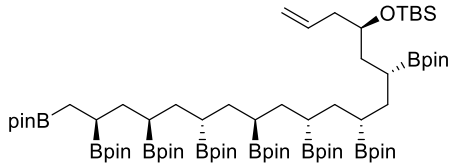

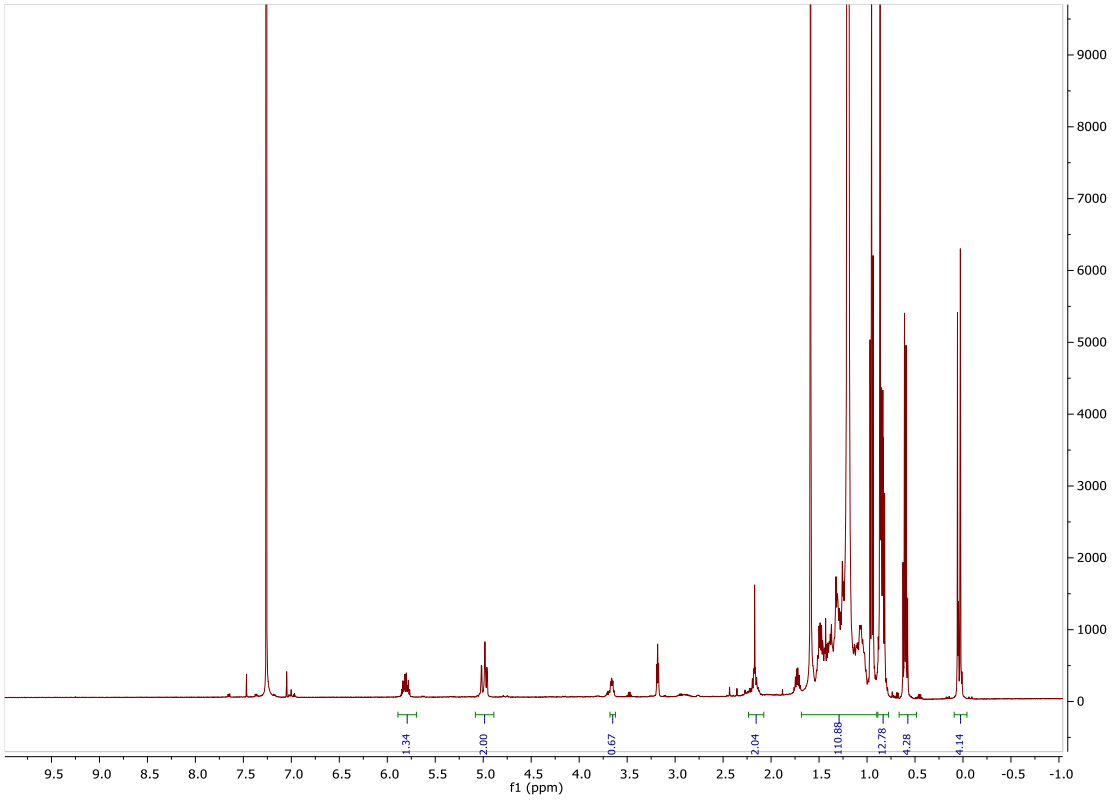

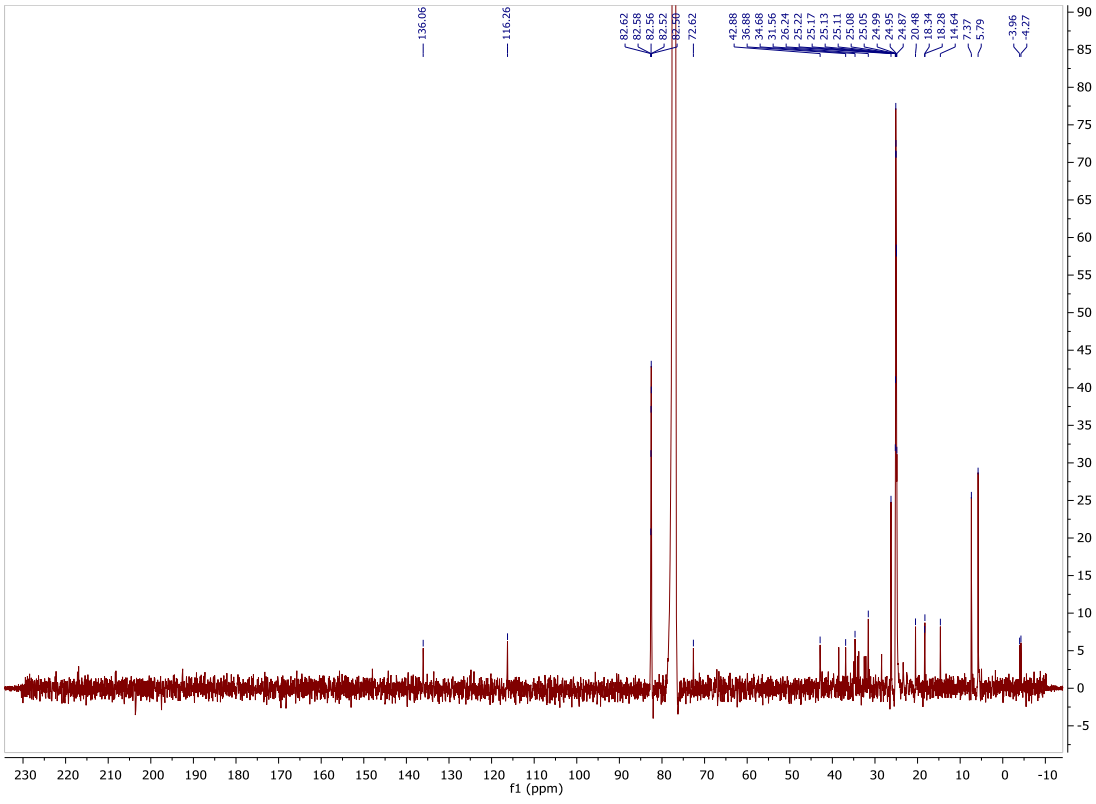

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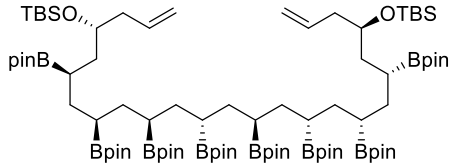
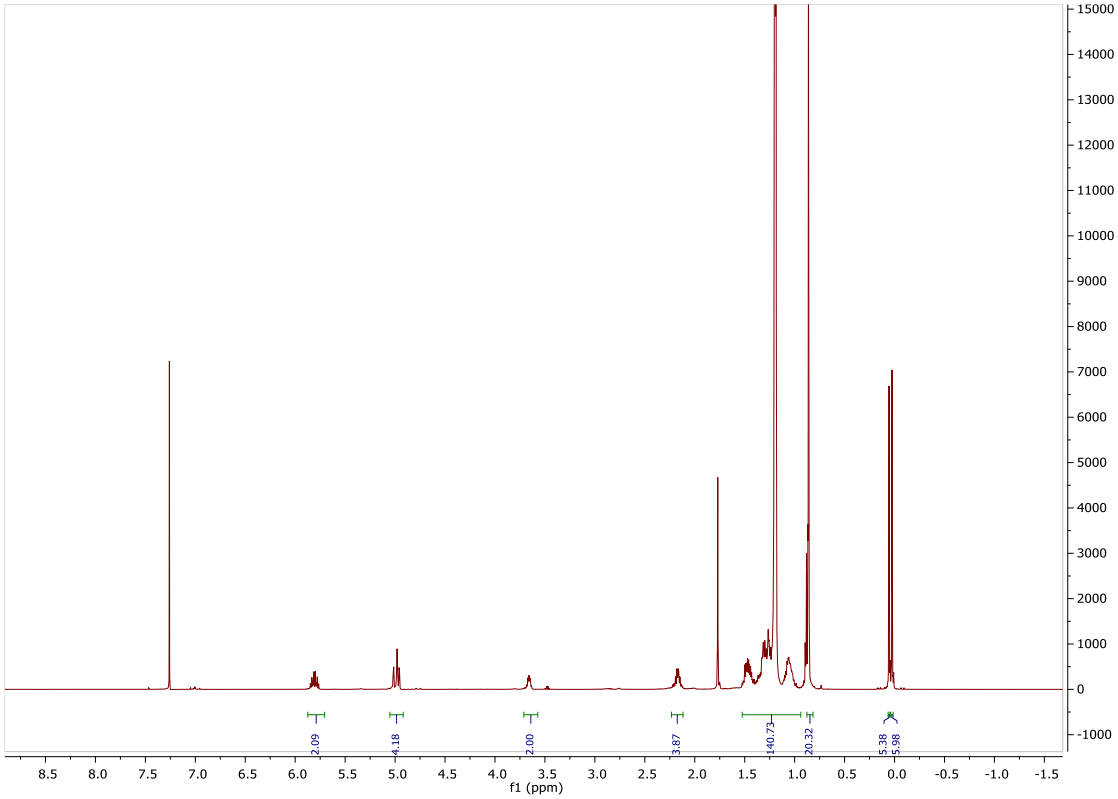
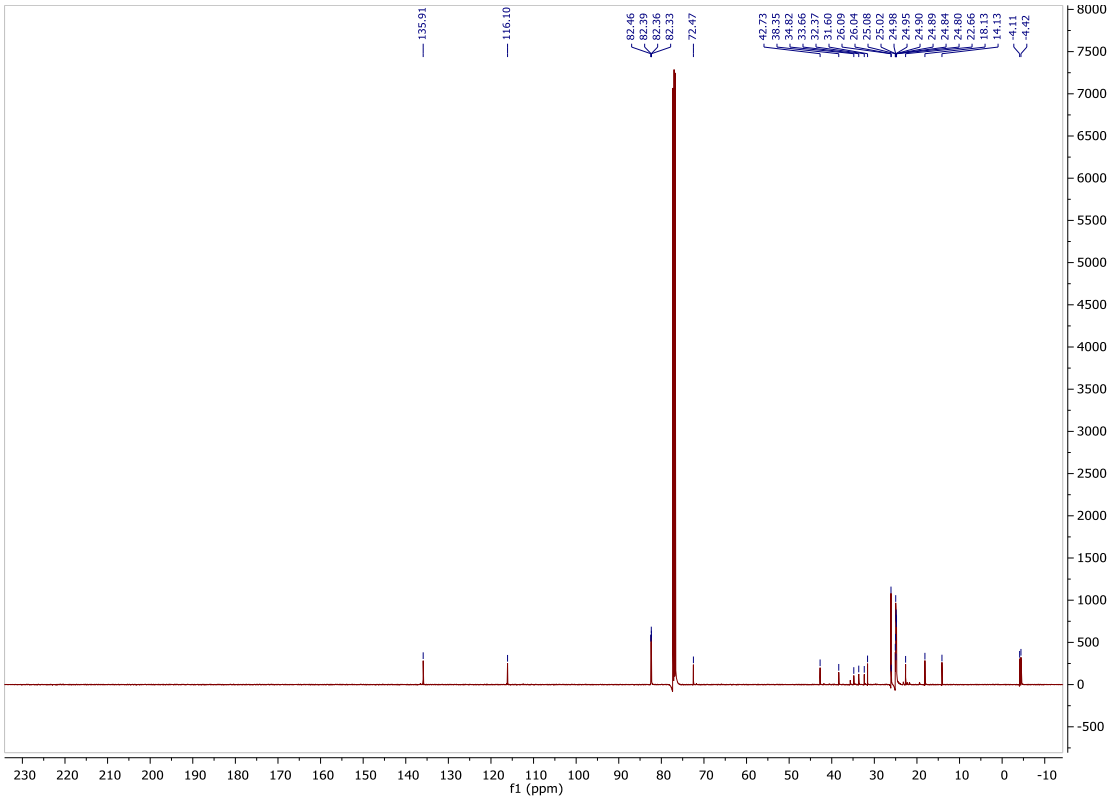
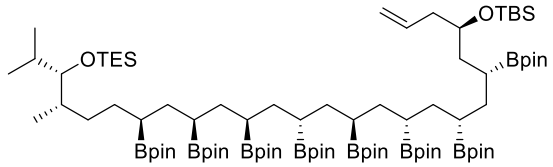
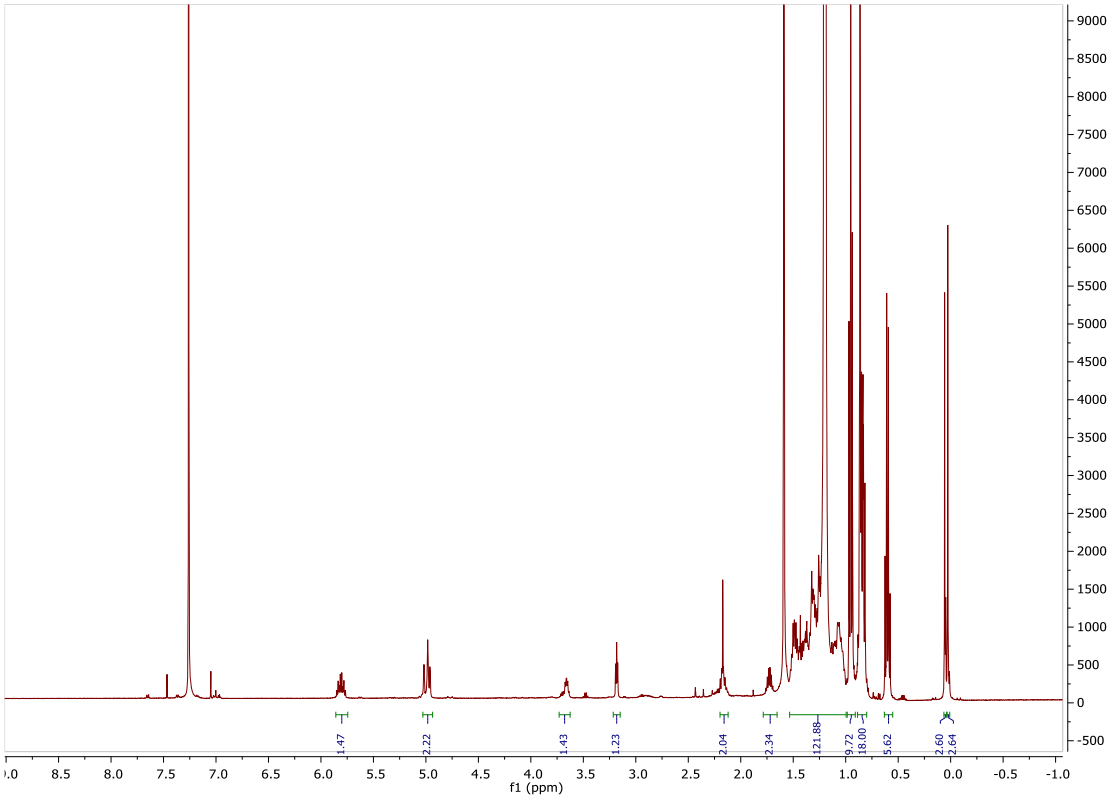


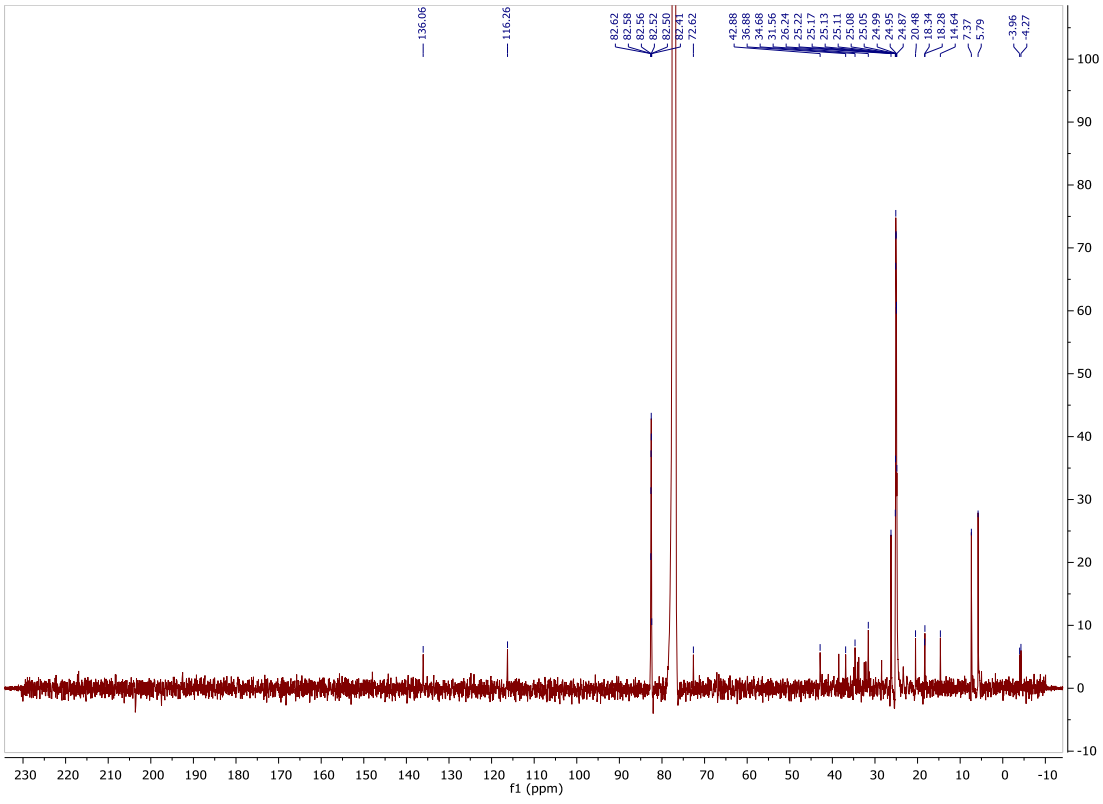




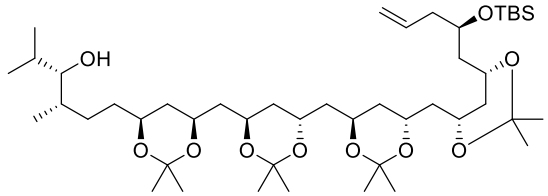
*Compound **500***

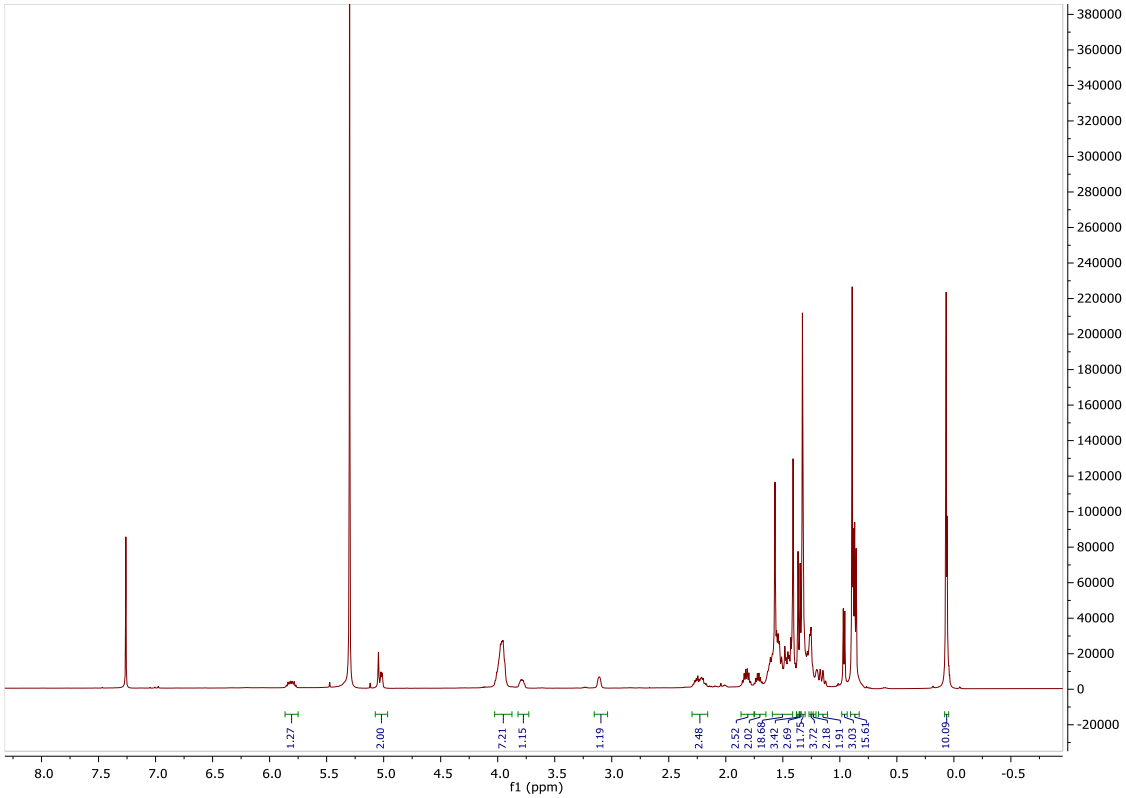


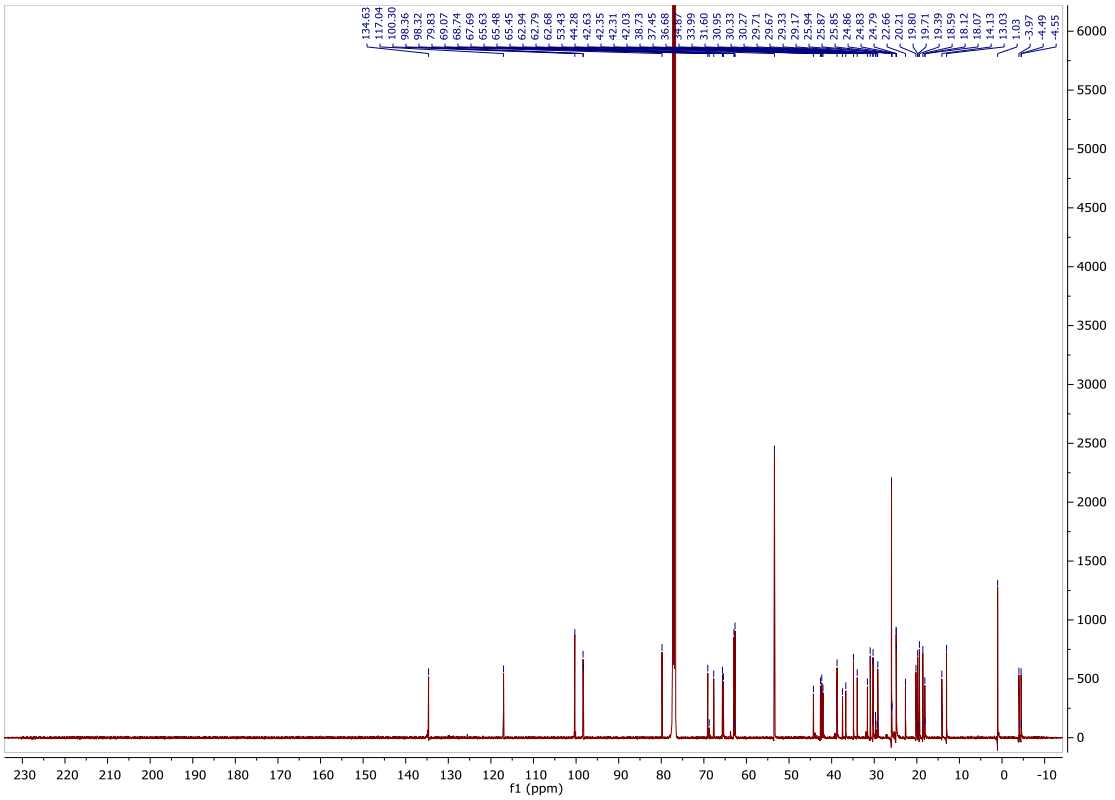




*Compound **494***



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62.79
62.68
53.43
44.28
42.63
42.35
42.31
42.03
38.73
37.45
36.68
34.87
33.99
31.60
30.95
30.33
30.27
29.71
29.67
29.33
29.17
25.94
25.87
25.85
24.86
24.83
24.79
22.66
20.21
19.80
19.71
19.39
18.59
18.12
18.07
14.13
13.03
1.03
-3.97
-4.49
-4.55
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)